Remarks

Reconsideration of this application is respectfully requested.

Claims 1, 4, 6, 8 and 11-26 are pending in the application, with claims 1 and 8 being the independent claims.

Claims 1 and 8 have been amended. Support for the amendment to claims 1 and 8 is found, for example, at paragraph [0001], page 1; paragraph [0014], pages 4-5; paragraph [0016], page 5; paragraph [0033], pages 8-9 and the abstract of the substitute specification filed on July 26, 2004 ("specification").

Claims 4, 6 and 11 have been amended to further conform the style of the claims to U.S. patent practice.

New claims 12-26, which depend from claim 1 or 8, have been added to claim additional embodiments of the independent claims. Claims 12 and 13 are directed to embodiments recited in claim 11. Support for claims 14-19 is found, for example, at paragraph [0001], page 1; paragraph [0014], pages 4-5; paragraph [0016], page 5; paragraph [0033], pages 8-9 and the abstract of the specification. Support for new claims 20-26 is found, for example, in Examples 1-4 of the specification.

The title has been amended in view of the pending claims.

These amendments are believed to introduce no new matter and their entry is respectfully requested.

In view of the above amendments and the following remarks, Applicant respectfully requests that the Examiner reconsider the outstanding rejection and that it be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

The rejection of claims 1, 4, 6, 8 and 11 under 35 U.S.C. § 103(a) as allegedly obvious over Seymour, A., *Manag. Care, 10*:11-16, 2001 ("Seymour") in view of McCall, A.L., *Expert Opin. Pharmacother., 2*:699-713, 2001 ("McCall") has been maintained. Office Action at p. 3. Applicant respectfully traverses the rejection for at least the reasons of record and the additional reasons that follow.

Legal Principles

Obviousness determinations under 35 U.S.C. § 103 are carried out according to the standard set forth by the United States Supreme Court in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 148 USPQ 459 (1966):

> [u]nder § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. As indicia of obviousness or nonobviousness, these inquiries may have relevancy.

Id. at 17-18, 148 USPQ at 467.

Seymour and McCall do not teach a composition comprising a synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios.

Independent claim 1 is directed to a solid pharmaceutical composition comprising, *inter alia*, a *synergistic* combination of glimepiride and metformin hydrochloride, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500, and wherein the combination of glimepiride and metformin hydrochloride

reduces blood glucose levels greater than either glimepiride or metformin hydrochloride alone. Independent claim 8 is directed a method of controlling blood glucose levels in a patient with type 2 diabetes, comprising, *inter alia*, administering to the patient a *synergistic* combination of glimepiride and metformin hydrochloride, in a solid dosage form, wherein the weight ratio of glimepiride and metformin hydrochloride is about 1/500, and wherein the combination of glimepiride and metformin hydrochloride reduces blood glucose levels greater than either glimepiride or metformin hydrochloride alone.

The Office states that Applicant's remarks filed on September 22, 2010 are not persuasive because Seymour and McCall both teach a combination of glimepiride and metformin. Office Action at p. 9. However, Seymour and McCall do not disclose a *synergistic* composition comprising a weight ratio of about 1/500 of glimepiride that reduces blood glucose levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone. Furthermore, Seymour and McCall do not provide a reason or rationale that would have lead a skilled artisan to conclude that a composition comprising a weight ratio of about 1/500 of glimepiride and metformin hydrochloride is synergistic and reduces blood glucose levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone.

Seymour provides a clinical overview for the treatment of diabetes with glyburide and metformin hydrochloride as an initial therapy or as a replacement therapy for patients who are inadequately controlled on monotherapy. Seymour at p. 16. Seymour further provides recommended Glucovance® (glyburide and metformin hydrochloride) starting doses for initial and replacement therapy (Table 2) and a conversion guide for switching patients, for example, from Amaryl® (glimepiride) and Glucophage®

(metformin hydrochloride) dual therapy to Glucovance® (Table 1). As such, Seymour does not disclose or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios.

According to the Office, McCall teaches that glimepiride is approved for use with metformin, glimepiride can be given at a dose of 1-8 mg as a monotherapy, and glimepiride may have certain advantages over glyburide. Office Action at pp. 4-6. However, McCall does not cure the deficiencies of Seymour because it does not disclose or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios.

At page 5 of the Office Action, the Office states that a person of skill in the art would have been motivated to substitute the glyburide component of Glucovance® with glimepiride because McCall teaches glimepiride has reduced hypoglycemic adverse effects and offers convenience, dosing flexibility and relatively low expense. McCall at p. 709, right col. and p. 710, right col. The Office indicates that Applicant's prior remarks are not persuasive because McCall provides a motivation to combine metformin and glimepiride, particularly "an identification of the superiority of glimepiride." Office Action at p. 11. The passages cited by the Office in this regard relate only to the effect of glimepiride in *reducing the adverse effect of hypoglycemia.* These passages do not disclose or suggest that a composition comprising a combination of glimepiride and metformin hydrochloride at the specified weight ratios is synergistic and reduces blood glucose levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone. Therefore, one of ordinary skill in the art reading

McCall would not have arrived at the claimed synergistic combination of glimepiride and metformin hydrochloride.

Additionally, publications available at the time the application was filed indicated combination therapy with metformin and sulfonylureas were being tested for compliance with the American Diabetes Association (ADA) guidelines. See Exhibit 1 (Miller *et al.*, *Diabetes Care*, *23*:444-448, 2000). Guidelines and algorithms for initiation and adjustment of therapy with metformin and sulfonylureas in the management of diabetes were later published by the ADA in 2006 and 2009, after the application was filed. See Exhibit 2 (Nathan *et al.*, *Diabetes Care, 29*:1963-1972, 2006) and Exhibit 3 (Nathan *et al.*, *Diabetes Care, 32*:193-203. As such, Exhibits 1-3 provide further support that one of ordinary skill in the art would not have been motivated to substitute the glyburide component of Glucovance® with glimepiride, because metformin and sulfonylurea combinations were still being tested for compliance ADA guidelines at the time the application was filed.

Thus, for at least these reasons, Applicant maintains that Seymour and McCall do not support a *prima facie* case of obviousness of the claims. As such, the obviousness rejection should be withdrawn.

The cited references at best provide an extremely large number of potential options upon which one of ordinary skill in the art could combine to arrive at a synergistic combination of glimepiride and metformin having the specified weight ratios.

The Supreme Court has stated,

> [w]hen there is a design need or market pressure to solve a problem and there are a *finite number* of identified, *predictable* solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp....[i]n that instance the fact that a

> combination was obvious to try might show that it was obvious under § 103.

KSR International Co. v. Teleflex, Inc., 127 S.Ct. 1727, 1741 (2007) (emphasis added). Also, the Federal Circuit has stated that "where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009).

In this instance, the cited references at best provide an extremely large number of potential options upon which one of ordinary skill in the art could combine to arrive at the claimed synergistic combination of glimepiride and metformin having the specified weight ratios that reduces blood glucose levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone. While the Office may hone in on particular active ingredients and dosages in the cited references using the claimed weight ratios as a starting point, this is applying hindsight reasoning in selecting which amounts of glimepiride and metformin hydrochloride of the numerous possible options to use as a starting point result in a synergistic combination. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); and *In re Gorman*, 933 F.2d 982, 18 USPQ2d 1885 (Fed. Cir. 1991) (stating it was impermissible to use applicant's structure as a template to select elements from a reference or references to fill in the gaps).

Therefore, for at least these reasons, Applicant maintains that Seymour and McCall do not support a *prima facie* case of obviousness of the claims. Accordingly, the obviousness rejection should be withdrawn.

Even if prima facie obviousness were established, evidence of unexpected results and commercial success exists that would overcome such a rejection.

Secondary considerations of non-obviousness include unexpected results and evidence of commercial success. *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S. Ct. 684, 694, 148 USPQ 459, 467 (1966). The Federal Circuit has reaffirmed that the USPTO must in all cases consider any evidence presented tending to support secondary considerations of non-obviousness. *In re John B. Sullivan and Findlay E. Russell*, 498 F.3d 1345, 84 USPQ2d 1034 (Fed. Cir. 2007). As discussed above, a *prima facie* case of obviousness has not been established with respect to the claims. Moreover, the record demonstrates that *prima facie* obviousness, even if it were established, would be negated by the unexpected properties and commercial success of the claimed invention, namely, the inventor's discovery of the claimed synergistic combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500, wherein the combination of glimepiride and metformin hydrochloride reduces blood glucose levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone.

Here, Applicant has discovered that compositions comprising a combination of glimepiride and metformin hydrochloride at a weight ratio of about 1/500 have an unexpectedly improved effect on reducing blood glucose levels in diabetic patients. Paragraphs [0012], [0014] and [0033] of the specification. As explained in the specification, the treatment of patients with compositions comprising a combination of glimepiride and metformin hydrochloride at a weight ratio of 1/500 resulted in unexpected decreases in glycosylated hemoglobin (HbA_{1C}), fasting plasma glucose levels, and prandial blood glucose levels compared to treatments with glimepiride or metformin alone. Paragraph [0033] of the specification. These data are reproduced in

the table below, along with data from U.S. Patent No. 6,011,049 which measured the same parameters following treatment with metformin and glyburide:

	Metformin 500 mg	**Glimepiride 1 mg**	**Metformin + Glimepiride 500 mg / 1mg**	Metformin + Glyburide 1500 mg / 20 mg (U.S. Pat. No. 6,011,049)
Glycosylated Hemoglobin (HbA_{1c})	+0.06	+0.25	**-0.70**	+0.10
Fasting Plasma Glucose (FPG)	+0.75	+0.68	**-1.77**	+6.0
Prandial Blood Glucose	+1.08	+0.99	**-2.7**	*not determined*

Specifically, the above data show that treatment with compositions comprising glimepiride and metformin, at a 1/500 weight ratio, resulted in a potentiated therapeutic efficacy that is unexpectedly greater than treatment with glimepiride or metformin alone. This potentiated effect was not observed with combined treatment of glyburide and metformin at significantly increased doses (20 times more sulfonylurea and three times more metformin). Thus, in view of the potentiated therapeutic efficacy observed with compositions comprising glimepiride and metformin at a 1/500 weight ratio, the claimed combinations of glimepiride and metformin would not have been predictable. As such, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection.

Exhibits A and B

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant reminds the Examiner of Exhibit A (González-Oritz *et al.*, *Rev. Inv. Clin.* 56:327-333, 2004; paragraph [0012] of the specification) submitted with the

Amendment and Reply Under 37 C.F.R. § 1.116 filed on April 6, 2009. As explained in the Abstract, Exhibit A provides data from a clinical study involving the treatment of diabetic patients with 4 mg of glimepiride alone, 2 g of metformin alone, or 4 mg of glimepiride and 2 g of metformin (1/500 weight ratio) together in the same composition. The efficacy criteria evaluated in the study were either a decrease in glycosylated hemoglobin (HbA_{1C}, or "A1C" in Exhibit A) of 1% or more, or a reduction in A1C of 7% or less. According to the Abstract, the decrease in A1C concentration was -0.9 ± 1.6% in the glimepiride group, -0.7 ± 2.1% in the metformin group, and -1.3 ± 1.8 mg/dL in the combined therapy group. Thus, only the combination therapy group attained the efficacy criteria of decreased A1C of 1% of more. Furthermore, the percentage of patients attaining the efficacy criteria of 1% or more or a reduction in A1C of 7% or less was markedly enhanced in the combination therapy group compared to the monotherapy groups, while the frequency of adverse events was similar for all treatment groups.

Applicant also reminds the Office of Exhibit B (González-Oritz *et al.*, *J. Diabetes Complications*) submitted with the Amendment and Reply Under 37 C.F.R. § 1.116 filed on April 6, 2009 as additional evidence in support of non-obviousness. Exhibit B provides data from a clinical study comparing the efficacy of glycemic control in patients treated with 1 mg of glimepiride and 500 mg of metformin (1/500 weight ratio) together in the same composition, to patients treated with 5 mg of glibenclamide (glyburide) and 500 mg of metformin together in the same composition. As detailed in Table 2, the percentage of patients who maintained glycemic control after 12 months of treatment, measured by A1C levels less than 7%, were markedly higher in the

glimepiride/metformin treatment groups compared to the glyburide/metformin treatment groups.

In sum, Exhibits A and B provide further support for the non-obviousness of the claimed subject matter because they provide evidence that the claimed combination of glimepiride and metformin unexpectedly met certain therapeutic efficacy criteria compared to monotherapy with glimepiride or metformin alone, or compared to combination therapy with metformin and another sulfonylurea agent. Therefore, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests this rejection be withdrawn.

Exhibit C

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant reminds the Office of Exhibit C submitted with the Amendment and Reply Under 37 C.F.R. § 1.116 filed on April 6, 2009. Exhibit C provides post-filing date data from a clinical study involving the treatment of patients with type II diabetes with a daily dose of 4 mg of glimepiride alone ("Glimepiride"), 2 g of metformin hydrochloride alone ("Metformin"), or a combination of 4 mg of glimepiride and 2 g of metformin hydrochloride (1/500 weight ratio) together in the same composition ("Glimepiride + Metformin"). Glycosylated hemoglobin (HbA_{1C}) levels were measured prior to treatment ("baseline") and the percent change in HbA_{1C} levels was determined by comparing baseline HbA_{1C} levels to HbA_{1C} levels after treatment. The combination therapy group attained a reduction of HbA_{1C} levels greater than the individual effects of

glimepiride or metformin hydrochloride treatment alone. Moreover, only the combination therapy group attained the efficacy criteria of decreased HbA_{1C} of 1% of more.

As such, Exhibit C provides further support for the non-obviousness of the claimed subject matter because it provides evidence of the synergistic effects of the claimed combination of glimepiride and metformin hydrochloride compared to monotherapy with glimepiride or metformin hydrochloride alone. Thus, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests this rejection be withdrawn.

Exhibit D

As further evidence in support of the non-obviousness of the claimed subject matter, Applicant reminds the Office of Exhibit D (Shimpi, R.D., *et al.*, *Int. J. PharmTech Res. 1*:50-61, 2009) provided in Reply Under 37 C.F.R. § 1.111 filed on August 24, 2009. Exhibit D provides data from a clinical study comparing the effects of metformin and glimepiride treatment with metformin and glibenclamide (glyburide) treatment in patients with type 2 diabetes. Specifically, patients were treated with compositions comprising 1000 mg of metformin and 10 mg of glyburide, or with compositions comprising 1000 mg of metformin and 2 mg of glimepiride (1/500 weight ratio). Exhibit D at page 53. After 12 weeks of treatment, reductions in HbA_{1C} levels were observed in both treatment groups; however, patients treated with metformin and glimepiride exhibited significantly reduced HbA_{1C} levels compared to patients treated with metformin and glyburide. Exhibit D at Figure 1. In addition, patients treated with

metformin and glimepiride exhibited significantly reduced fasting plasma glucose (FPG) levels compared to patients treated with metformin and glyburide. Exhibit D at Figure 2.

As such, Exhibit D provides further support for the non-obviousness of the claimed subject matter because it provides evidence that the claimed compositions comprising glimepiride and metformin at the specified weight ratios unexpectedly met certain therapeutic efficacy criteria compared to therapy with metformin and glyburide.

Exhibit E

In further support of the non-obviousness of the claimed invention, Applicant reminds the Office of the Declaration Under 37 C.F.R. § 1.132 by Gerardo Gustavo Gómez Bustos ("Declaration") filed with the Reply Under 37 C.F.R. § 1.116 filed on September 22, 2010 as evidence of the success of commercial products within the scope of the presently claimed pharmaceutical compositions. In the Declaration, Gerardo Gustavo Gómez Bustos indicates that Silanes has successfully developed, manufactured and marketed several commercial products having a 1/500 weight ratio of glimepiride/metformin hydrochloride. Declaration at paragraph 2. These products have a significant market presence throughout Mexico, Central America and South America and are the subject of significant licensing and co-marketing agreements between Silanes and third party companies. Declaration at paragraphs 3-8. In addition, these products have been recognized with national awards for innovation, and represent the *first time* a medicine developed in Mexico has been licensed to a transnational company for world-wide sale. Declaration at paragraphs 7-10. It is Gerardo Gustavo Gómez Bustos's opinion that the commercial success of Silanes' commercial products is due to their unique features which were desired by the anti-diabetic market (*i.e.*, a composition

comprising glimepiride and metformin together in one tablet, in a synergistic ratio) and were not previously known or available.

Also, after introduction of Silanes' commercial product, the number of prescriptions increased from 2002 through 2007, and sales of Silanes' commercial product remained consistent from 2005 through 2010, with notable increases in sales from 2005 through 2007 and from 2009 through 2010. Declaration at paragraph 11 and Figures 1-2. It is Gerardo Gustavo Gómez Bustos's opinion that these trends in the number of prescriptions and sales were not the result of increased advertising of Silanes' commercial products. It is also Gerardo Gustavo Gómez Bustos's opinion that the commercial success of Silanes' commercial products is due to their unique features which were desired by the anti-diabetic market (*i.e.*, a composition comprising glimepiride and metformin together in one tablet, in a synergistic ratio) and were not previously known or available.

At page 14 of the Office Action, the Examiner appears to acknowledge that evidence of non-obviousness is available for the claimed invention, but that the evidence of non-obviousness does not outweigh the evidence of obviousness in view of the teachings in the cited art. Even if such evidence of obviousness were present, Applicant submits that the evidence of non-obviousness of record along with the additional evidence of non-obviousness presented herein, is significant enough to establish the non-obviousness of the claimed invention in view of recent USPTO guidance and Federal Circuit case law as explained in detail in Applicant's Reply Under 37 C.F.R. § 1.116 filed on September 22, 2010.

Thus, even if a *prima facie* case of obviousness were established, which it has not, Applicant respectfully contends that these unexpected results and commercial would be sufficient to overcome such a rejection. For at least these reasons, Applicant respectfully requests the obviousness rejection be withdrawn.

Claims 4 and 12

Claims 4 and 12 depend from independent claims 1 and 8, respectively, and state that the composition comprises 500 mg of metformin hydrochloride and 1 mg of glimepiride. Seymour does not disclose glimepiride dosages less than 2 mg. McCall only discloses 1 mg dosages of glimepiride as a monotherapy. Seymour and McCall do not disclose, or provide a reason or rationale that would have lead a skilled artisan to use, 1 mg of glimepiride in a synergetic composition comprising a combination of glimepiride and metformin hydrochloride. As such, claims 4 and 12 are allowable for at least the reasons set forth above, and further in view of their own respective distinguishing features.

Claims 14 and 15

Claims 14 and 15 depend from independent claims 1 and 8, respectively, and state that the composition reduces blood glucose levels in a patient with type 2 diabetes greater than the additive effect of glimepiride and metformin hydrochloride alone. As explained above, Seymour and McCall do not disclose or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios. In addition, Seymour and McCall do not disclose or suggest that the effect on blood

glucose levels in a patient with type 2 diabetes is greater than additive. Therefore, claims 14 and 15 are allowable for at least the reasons set forth above, and further in view of their own respective distinguishing features.

Claims 16 and 17

Claims 16 and 17 depend from independent claims 1 and 8, respectively, and state that the combination of glimepiride and metformin hydrochloride reduces glycosylated hemoglobin levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone. As explained above, Seymour and McCall do not disclose or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios. In addition, Seymour and McCall do not disclose or suggest that a combination of glimepiride and metformin hydrochloride reduces glycosylated hemoglobin levels in a patient with type 2 diabetes greater than either glimepiride or metformin hydrochloride alone. Therefore, claims 16 and 17 are allowable for at least the reasons set forth above, and further in view of their own respective distinguishing features.

Claims 18 and 19

Claims 18 and 19 depend from independent claims 1 and 8, respectively, and state that the composition reduces glycosylated hemoglobin levels in a patient with type 2 diabetes greater than the additive effect of glimepiride and metformin hydrochloride alone. As explained above, Seymour and McCall do not disclose or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified

weight ratios. In addition, Seymour and McCall do not disclose or suggest that the effect on glycosylated hemoglobin levels in a patient with type 2 diabetes is greater than additive. Therefore, claims 18 and 19 are allowable for at least the reasons set forth above, and further in view of their own respective distinguishing features.

Claims 20-26

Claims 20 and 21 depend from independent claim 1 and state that the composition contains certain excipients found, for example, in the compositions of the examples and in compositions related to the evidence of secondary indicia of nonobviousness presented herein. Claims 22-24 depend from claim 1 and state that the composition contains certain amounts of certain excipients found, for example, in the compositions of the examples and in compositions related to the evidence of secondary indicia of nonobviousness presented herein. Claims 25 and 26 depend from claims 4 and 6, respectively, and state that the composition contains certain amounts of certain excipients found, for example, in the compositions of the examples and in compositions related to the evidence of secondary indicia of nonobviousness presented herein.

As explained above, Seymour and McCall do not disclose or suggest the claimed synergistic combination of glimepiride and metformin hydrochloride at the specified weight ratios. In addition, Seymour and McCall do not disclose or suggest the excipients or amounts of excipients specified in claims 20-26 that are found in the compositions of the examples and in compositions related to the evidence of secondary indicia of nonobviousness presented herein. Therefore, claims 20-26 are allowable for at least the

reasons set forth above, and further in view of their own respective distinguishing features.

Conclusion

The stated ground of rejection has been properly traversed. Applicant therefore respectfully requests that the Examiner reconsider the presently outstanding rejection and that it be withdrawn. Applicant believes that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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1494952v2

Exhibit 1

Meeting American Diabetes Association Guidelines in Endocrinologist Practice

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OBJECTIVE — To determine whether American Diabetes Association (ADA) guidelines can be met in the context of routine endocrinology practice.

RESEARCH DESIGN AND METHODS — Charts were reviewed for a group of patients who were examined in 1998, followed for ≥1 year, and had two or more visits during that year. Process measures and metabolic outcomes were studied for patients with type 2 diabetes, and glycemic control was assessed for patients with type 1 diabetes.

RESULTS — A total of 121 patients with type 2 diabetes had a mean age of 63 years, a mean BMI of 31 kg/m^2, and a mean duration of diabetes of 12 years. Many had comorbidities or complications: 80% had hypertension, 64% had hyperlipidemia, 78% had neuropathy, 22% had retinopathy, and 21% had albuminuria. Management of type 2 diabetic patients was complex: 38% used oral hypoglycemic agents alone (54% of these were using two or more agents), 31% used oral hypoglycemic agents and insulin, and 26% used insulin alone; 42% of patients taking insulin therapy injected insulin three or more times per day. Within 12 months, 74% of patients had dilated eye examinations, 70% had lipid profiles, and 55% had urine albumin screening. Of the patients, 87% had a foot examination at their last visit. Blood pressure levels averaged 133/72 mmHg, cholesterol levels averaged 4.63 mmol/l, triglyceride levels averaged 1.99 mmol/l, HDL cholesterol levels averaged 1.24 mmol/l, and LDL cholesterol levels averaged 2.61 mmol/l. Random blood glucose levels averaged 8.0 mmol/l, and HbA_{1c} levels averaged 6.9 ± 0.1%. A total of 87% of patients had HbA_{1c} levels ≤8.0%. A total of 30 patients with type 1 diabetes had mean age of 44 years, a mean BMI of 26 kg/m^2, and a mean duration of diabetes of 20 years. All type 1 diabetic patients used insulin and averaged 3.4 injections a day; their average HbA_{1c} level was 7.1 ± 0.2%, and 80% had HbA_{1c} levels ≤8.0%.

CONCLUSIONS — Although endocrinologists must manage patients with multifaceted problems, complex treatment regimens yield glycemic control levels comparable with the Diabetes Control and Complications Trial and allow ADA guidelines to be met in a routine practice setting.

Diabetes Care 23:444–448, 2000

Strong evidence exists that good diabetes management results in significant benefits. In 1993, the Diabetes Control and Complications Trial (DCCT) showed that intensive insulin treatment significantly reduced the development and progression of microvascular complications in patients with type 1 diabetes (1). Both the Kumamoto Study (2) and the U.K. Prospective Diabetes Study (UKPDS) (3) showed that intensive therapy reduced microvascular complications in patients with type 2 diabetes as well. Evidence also exists that aggressively managing cardiovascular risk factors in patients with diabetes is beneficial. A subgroup analysis of the Scandinavian Simvastatin Survival Study (4) showed that patients with diabetes who took simvastatin had a significant reduction in major coronary heart disease events, and the UKPDS found that tight blood pressure (BP) control in patients with type 2 diabetes reduced the risk of stroke, microvascular disease, and deaths related to diabetes (5).

Despite such reinforcement for aggressive management, many patients continue to receive suboptimal care. Although the American Diabetes Association (ADA) guidelines for desired HbA_{1c} values, lipid and BP goals, and screening procedures have been widely distributed, these goals often are not met in the primary care settings where most patients receive their diabetes care (6–10). However, few studies have focused on specialist practice, and whether specialists are able to meet ADA guidelines is not clear. In 1995, the Medical Outcomes Study (11) found no "meaningful differences" in health outcomes (including glycemic control) in patients with diabetes who were treated by specialists or generalists. On the other hand, the DCCT showed that specialists could achieve good results in diabetes management in a study setting at a substantial cost (12). In short, limited evidence shows that diabetes specialists can meet ADA guidelines in routine practice. To determine whether DCCT-level glycemic control and adequate screening can be attained in this context, we assessed the quality of care for patients with diabetes managed by academic endocrinologists at the Emory Clinic.

RESEARCH DESIGN AND METHODS

The Emory Clinic in Atlanta, Georgia, includes the main outpatient practices of full-time Emory University faculty members on the staff of Emory University Hospital, which is a tertiary care referral center. The patient population varies in age, ethnicity, income level, and

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S.D.R. holds stock in Novo-Nordisk, a company that that manufactures products related to the treatment and management of diabetes.

Abbreviations: ADA, American Diabetes Association; BP, blood pressure; DCCT, Diabetes Control and Complications Trial; NHANES III, Third National Health and Nutrition Examination Survey; UKPDS, U.K. Prospective Diabetes Study.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

level of education. Of the patients at the Emory Clinic, 36% receive Medicare benefits, and 4% receive Medicaid. The Diabetes Unit at the time of this study was staffed primarily by two endocrinologists, two nurse practitioners, and a registered dietitian. Other endocrinologists examined ~15% of patients in the Diabetes Unit during the study period. Although the Emory Clinic is an academic setting, the physicians involved are expected to support their salaries with patient care efforts. This usually results in a physician examining 12–18 patients during each half day at the clinic.

Management overview

Although no set protocol exists, patients with type 2 diabetes are generally managed with individualized progressive intensification of therapy. Diet and exercise are encouraged with oral hypoglycemic agents as the initial pharmacological therapy. If patients exhibit poor glycemic control despite combinations of oral hypoglycemic agents, then insulin is frequently started with NPH insulin at bedtime. Finally, two or more daily insulin injections are used as needed to maintain tight glycemic control.

Physicians see patients in conjunction with nurse practitioners; visits with both physicians and nurse practitioners generally alternate with visits with nurse practitioners alone. Patients also have direct telephone access to nurse practitioners should patients have problems. The extensive use of physician extenders allows more frequent contact with patients and adjustment of therapy between office visits. Data from each visit are recorded on a flow sheet that stays with the patient's chart to allow easy review of laboratory data, screening tests, and medications. No formal system is in place to remind providers when screening tests are due.

Patients

By using the physicians' schedule data, charts were reviewed beginning with patients who had been seen most recently in December 1998. Working back through 1998, charts were examined until ~120 patients who met the inclusion criteria for type 2 diabetes were found. Assignment to the type 2 diabetes group was based on clinical criteria such as onset of diabetes at an age >30 years, current or prior use of noninsulin diabetes therapy, obesity, and lack of a history of diabetic ketoacidosis. Patients were included if they had seen the same endocrinologist (L.S.P. or S.S.P.G.) for at least 1 year (to allow time for clinical practices to take effect) and had at least two visits during that year (to exclude patients who had only a single visit). Although the focus of the study was patients with type 2 diabetes, those patients encountered during chart review who had type 1 diabetes were included in a separate analysis.

Main data outcomes

Primary data for patients with type 2 diabetes included the most recent HbA_{1c}, random plasma glucose, and lipid profiles; whether patients had a dilated eye examination by an eye specialist, a urine albumin assessment, or a lipid profile within the last year; and whether patients had a foot examination recorded at their most recent visit. Treatment regimens were also assessed. In addition, rates of peripheral neuropathy, albuminuria, retinopathy, hypertension, hyperlipidemia, coronary artery disease, and peripheral vascular disease for the population were determined. Because of the small number of patients with type 1 diabetes, analysis of their data was limited to HbA_{1c} values and insulin regimens. Data were collected primarily from the flow sheet, but when these sheets were incomplete, office notes were examined. Finally, when demographic information could not be obtained from the chart (e.g., date of onset of diabetes), the patient was contacted directly by telephone. Telephone contact was necessary for <15% of patients.

Identifying complications

Most complications could be assessed from the flow sheet or from the most recent clinic note. Patients were classified as having a complication if it was included in the problem list in previous notes or if other criteria were met, including the following. First, peripheral neuropathy was diagnosed if vibratory sense at the distal end of the first metatarsal was <15 s or if the patient failed the standard 10-g filament test. Second, albuminuria was diagnosed if albumin excretion was >30 mg/24 h or if a spot urine albumin/creatinine ratio was >0.030 mg/mg. Third, diagnosis of retinopathy was based on patient self-reports from eye specialist visits or a history of laser or surgical therapy. Fourth, hypertension was diagnosed if the patient had been taking antihypertensive medication (other than ACE inhibitors if the patient had albuminuria) or if a recent BP measurement was >130/85 mmHg. Fifth, coronary artery disease was diagnosed if problems such as angina, congestive heart failure, or myocardial infarction were included in the problem list. Sixth, hyperlipidemia was diagnosed if the patient was taking lipid-lowering medication, if a recent LDL cholesterol measurement was ≥3.36 mmol/l (130 mg/dl), or if a recent triglyceride level was ≥2.26 mmol/l (200 mg/dl) (per ADA guidelines that were operative in 1998) (13). Finally, peripheral vascular disease was diagnosed if the clinic notes documented diminished peripheral pulses, carotid bruits, or carotid or lower-extremity vascular surgery or if the patient had a history of nontraumatic amputation without evidence of peripheral neuropathy.

Laboratory data measurement

More than 90% of patients had HbA_{1c} values measured in the clinic with the DCA 2000 (Bayer, Elkhart, IN; normal range 3.4–6.2%). Of the 14 patients who did not have HbA_{1c} levels measured in the clinic, 10 had the test performed at Emory University Hospital (where the upper limit of normal is also 6.2%). Random glucose values during clinic visits (virtually all postprandial) were obtained using the One Touch II meter (Lifescan; Johnson & Johnson, Milpitas, CA). All other evaluations were performed using standard methodology either in the Emory University Hospital laboratory or in outpatient referral laboratories.

Statistical analysis

Statistical analysis was carried out with Statview 5.0 (SAS Institute, Cary, NC). Analysis of variance and unpaired two-tailed t tests were used to compare means between subgroups of patients. P values <0.05 were considered to be significant.

RESULTS

Demographics

A total of 151 patients were included in the study, and 80% had type 2 diabetes. Patients with type 2 diabetes were 53% men, were 26% African-American, had an average age of 63 years, had an average duration of diabetes of 12 years, and had an average BMI of 31 kg/m^2. The median number of visits was 4 (range 2–14) within the 12 months surveyed. For patients with type 1 diabetes, the average age was 44 years, the average duration of diabetes was 20 years, and the average BMI was 26 kg/m^2. Equal numbers of male and female patients had type 1 diabetes, and they were seen a median of four times (range 2–9).

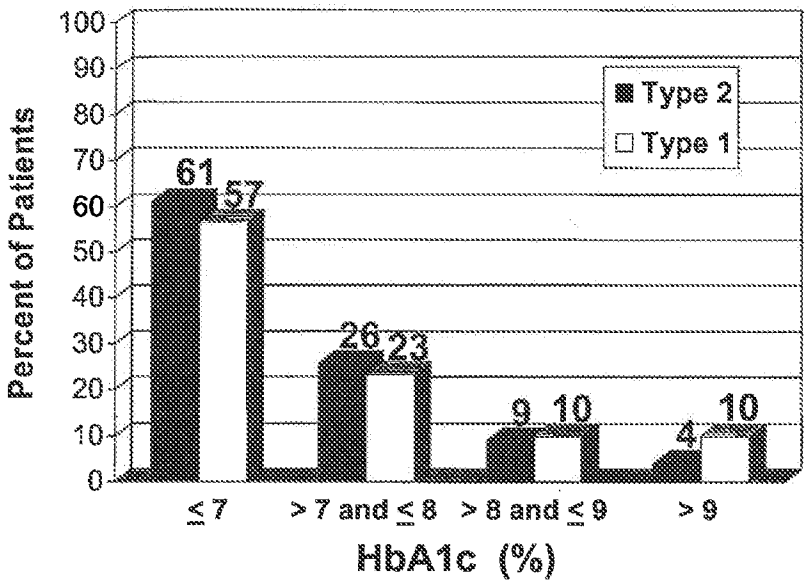

Figure 1—Distribution of HbA_{1c} values for type 2 (n = 121) and type 1 (n = 30) diabetic patients.

Diabetes complications

Many patients with type 2 diabetes had complications from their diabetes, and comorbidities were common. A total of 78% had peripheral neuropathy, 22% had retinopathy, 21% had albuminuria, 80% had hypertension, 64% had hyperlipidemia, 27% had coronary artery disease, and 14% had peripheral vascular disease.

Screening for diabetes complications

Screening studies in most patients with type 2 diabetes approached ADA guidelines. The rate of documented foot examinations at the most recent visit was highest at 87% of patients, followed by dilated eye examinations within the past year (74%) and lipid profiles within the past year (70%). Urine albumin screening was performed least frequently, with measurements within the past year in 55% of patients.

Metabolic outcomes

Patients with type 2 diabetes had an average BP level of 133/72 mmHg, an average cholesterol level of 4.63 mmol/l (179 mg/dl), an average triglyceride level of 1.99 mmol/l (176 mg/dl), an average HDL cholesterol level of 1.24 mmol/l (48 mg/dl), and an average LDL cholesterol level of 2.61 mmol/l (101 mg/dl). A total of 65% of patients were taking antihypertensive medications; of those, 62% had a BP level of ≤140/90 mmHg, and 41% had a BP level of ≤130/85 mmHg. A total of 55% of patients had been taking lipid-lowering medications. In patients taking lipid-lowering medication, the total cholesterol level averaged 4.55 mmol/l (176 mg/dl), the triglyceride level averaged 2.10 mmol/l (186 mg/dl), the HDL cholesterol level averaged 1.24 mmol/l (48 mg/dl), and the LDL cholesterol level averaged 2.48 (96 mg/dl). In patients not taking lipid-lowering medications, the total cholesterol level averaged 4.78 mmol/l (185 mg/dl), the triglyceride level averaged 1.77 mmol/l (157 mg/dl), the HDL cholesterol level averaged 1.27 mmol/l (49 mg/dl), and the LDL cholesterol level averaged 2.82 mmol/l (109 mg/dl). For patients with type 2 diabetes, the random blood glucose level averaged 8.0 mmol/l (144 ± 6 mg/dl), and the HbA_{1c} level averaged 6.9 ± 0.1%. A total of 61% of patients with type 2 diabetes had HbA_{1c} levels ≤7.0%, 87% had HbA_{1c} levels ≤8.0%, and 4% had HbA_{1c} levels >9% (Fig. 1). Patients managed with diet therapy alone had significantly lower HbA_{1c} values (5.7%) than patients managed with a combination of oral hypoglycemic agents and insulin or insulin alone (both groups 7.2%; $P < 0.05$ vs. diet alone). HbA_{1c} levels for patients managed only with oral hypoglycemic agents (6.6%) did not differ significantly from the other groups. No difference in HbA_{1c} level was evident based on sex, race, duration of diabetes, or age (patients aged ≥65 vs. <65 years).

Management

The management of patients with type 2 diabetes was complex, and nearly all patients required pharmacological therapy (Fig. 2). Very few patients (5%) were managed with diet therapy alone. A total of 38% were managed with oral hypoglycemic agents alone, and 54% of these patients used more than one agent. The most common combinations of oral therapy were sulfonylurea/metformin (21% of the total patients managed with oral hypoglycemic agents alone) and sulfonylurea/troglitazone (17%). Of the patients, 57% were using insulin (either alone or in combination with oral hypoglycemic agents). Of those using insulin and oral hypoglycemic agents, 46% were taking an insulin sensitizer (metformin or troglitazone). Patients using any insulin averaged 64 U/day (0.68 U · kg^{-1} · day^{-1}), and 42% were taking three or more daily injections. Overall, most patients (78%) required more than diet or a single oral hypoglycemic agent for adequate control.

Type 1 diabetes

All patients with type 1 diabetes were managed with insulin. They averaged 49 U (0.66 U · kg^{-1} · day^{-1}) of insulin and 3.4 injections per day, and 87% were taking three or more daily injections. The mean HbA_{1c} level for patients with type 1 diabetes was 7.1 ± 0.2%. A total of 57% of patients with type 1 diabetes had HbA_{1c} levels ≤7.0%, 80% had HbA_{1c} levels ≤8.0%, and 10% had HbA_{1c} levels >9% (Fig. 1). Again, no significant difference was evident in HbA_{1c} levels based on sex, race, duration of diabetes, or age.

CONCLUSIONS — This study provides evidence that ADA guidelines and DCCT-level glycemic control can be achieved in specialist practice. Although comorbidities and diabetes complications were frequent, patients with type 2 diabetes had good glycemic control. Complex treatment regimens were necessary; only 22% of patients were treated solely with diet therapy or a single oral hypoglycemic agent. Most patients had appropriate screening examinations, and BP and lipid outcomes were also good.

These findings contrast with previous studies that were based mostly on patients in primary care settings and that often have shown glycemic control to be relatively poor. Martin et al. (6) studied 378 patients with type 2 diabetes in 1992–1993 and found that mean HbA_{1c} values ranged from 8.6% in whites to 9.4% in blacks and 9.8% in Hispanics. In 1994, Weatherspoon et al.

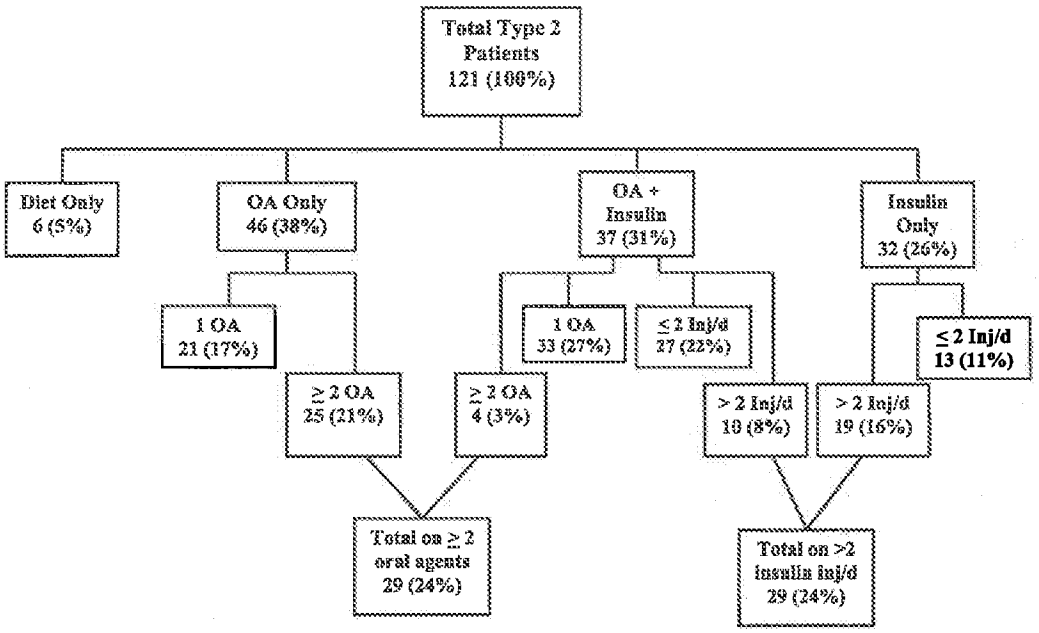

Figure 2—Distribution of therapy for patients with type 2 diabetes. Values (%) of total type 2 patients. Inj/d, injections of insulin per day; OA, oral hypoglycemic agent.

(7) reported that nearly 40% of patients with type 2 diabetes had HbA_{1c} values of ≥8%. We found no significant difference in HbA_{1c} levels based on race, and only 15% of our patients with type 2 diabetes had HbA_{1c} levels of ≥8%. Most recently, Harris et al. (8) found a mean HbA_{1c} level of 7.6% in patients with diabetes in the Third National Health and Nutrition Examination Survey (NHANES III), but patients using only oral hypoglycemic agents (46% of patients) averaged HbA_{1c} levels of 8.0%, and patients using any insulin (27% of patients) averaged HbA_{1c} levels of 8.3%. In comparison, our group taking oral hypoglycemic agents only had average HbA_{1c} levels of 6.6%, and patients using any insulin had average HbA_{1c} levels of 7.2%.

Improved glycemic control in this study may be attributable to our use of complex therapeutic regimens. Although similar numbers of patients were using oral hypoglycemic agents only (38 vs. 46% in the study by Harris et al. [8]) and insulin only (26 vs. 24%), substantially fewer of our patients were using diet therapy alone (5 vs. 27%), and substantially more were using oral hypoglycemic agents plus insulin (31 vs. 3%). In addition, more of our insulin-treated patients were injecting insulin three or more times a day (42 vs. ~4%) (8). Although we found that good control could be obtained with insulin dosages averaging only 0.7 $U \cdot kg^{-1} \cdot day^{-1}$, insulin needs were likely reduced by the concomitant use of oral hypoglycemic agents.

In addition to metabolic outcomes, process measures are also important in good diabetes care. Screening rates in our patients with type 2 diabetes were generally good, especially for eye examinations and lipid profiles, and were somewhat higher than those previously reported for several groups of patients from large claims databases. In two studies of Medicare patients, 40–46% of patients had ophthalmological examinations, and 55–56% had lipid measurements during a 1-year period (9,10). Martin et al. (6) found that 53–66% of patients had annual ophthalmological examinations, 52–62% had at least one total cholesterol and one HDL cholesterol measurement during a 2-year period, and 56–63% had at least two urine dipstick tests during a 2-year period. Another study reported that 48% of 353 patients with diabetes had urine protein screenings (test not specified), but 92% had no documented foot examinations during a 1-year period (14).

Our data are not the first to suggest that specialists may be able to meet ADA guidelines better than primary care practice physicians. Ho et al. (15) have shown that process measures are addressed better by specialists, and Hellman et al. (16) achieved a median HbA_{1c} level of 7.3% in patients who had received long-term care in their specialty practice. However, we believe our study is the first report to assess patient complexity and details of management in specialist practice.

The discrepancies between our data and those of primary care studies may be because of factors other than the type of treating physician. First, data used in the studies mentioned above are principally from the early 1990s and may not reflect current practices. Second, rapid on-site HbA_{1c} measurements are used routinely in our practice and may play a role in improving glucose control (17). We may have been referred and retained patients who are more motivated and therefore achieve better results. Although our self-selected population cannot be compared directly with inclusive surveys such as NHANES III, our patients have a longer duration of diabetes than the NHANES III population (8), which makes our patients potentially more difficult to manage (3). We believe that good glycemic outcomes are attributable to a commitment to achieving normal metabolic status that is reinforced through multiple contacts, including not only physician appointments but also nurse practitioner visits, dietitian visits, and telephone calls.

BP levels in our patients averaged 133/72 mmHg, which may reflect difficulty in regulating systolic BP in a popula-

tion with a 78% prevalence of neuropathy. All patients were not tested for diabetes complications during the 12 months of survey, and urine albumin screening was documented for only 55% of the patients, even though evaluation of convenient spot urine samples was common. Apparent failure to meet national guidelines may reflect the true limitations of our practice, but analysis was based largely on data recorded by hand in patient flow sheets and may have underestimated actual performance.

Other limitations of our study include its retrospective nature. In some cases, complications noted in the problem list could not be confirmed with the limited data available; for example, we do not know the actual retinal status of patients who did not have dilated eye examinations within the previous year and who were not described as having retinopathy previously. Also, our results may be population specific. The study population may have been biased toward those patients who had resources that permitted a median of four visits per year. Data on level of income and education were not collected, but a limited analysis of 50 patients who did not meet the study inclusion criteria revealed no significant differences in demographic characteristics, insurance mix, or HbA_{1c} level between the study sample and the excluded patients. In addition, review of on-site data from all clinic patients seen from October to December 1998 showed that follow-up patients who were not included in the study averaged HbA_{1c} levels of 7.1% (similar to levels in our study population) and that new patients during that period averaged HbA_{1c} levels of 8.5%, which is significantly higher than follow-up patients included or not included in the study. Thus, this study appears to be an accurate representation of our practice. Another limitation is the lack of data on the prevalence of hypoglycemia. Although we believe that severe hypoglycemia is uncommon in our patients, many patients using sulfonylureas or insulin report intermittent glucose levels of ~3 mmol/l (50–60 mg/dl). Finally, we were not able to assess the costs associated with our results.

In conclusion, we have shown that, in the context of routine specialist practice, achieving good control of glucose, BP, and lipid levels outside of a study protocol is possible, but to do so, complex treatment regimens are required. Achieving substantial rates of screening for diabetes complications is likewise possible. Our data suggest that differences may exist in diabetes management in specialist versus generalist settings. Because the Medical Outcomes Study reflected patient management from 1986 to 1993 (largely before the completion of the DCCT) and included relatively few patients with diabetes and few endocrinologists (11), new prospective studies are needed to compare concurrent management, outcomes, and costs for the diabetes care given by specialists and generalists.

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Exhibit 2

Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes

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The epidemic of type 2 diabetes in the latter part of the 20th and in the early 21st century, and the recognition that achieving specific glycemic goals can substantially reduce morbidity, have made the effective treatment of hyperglycemia a top priority (1–3). While the management of hyperglycemia, the hallmark metabolic abnormality associated with type 2 diabetes, has historically had center stage in the treatment of diabetes, therapies directed at other coincident features, such as dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance, have also been a major focus of research and therapy. Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to have a powerful beneficial impact on diabetes-specific complications, including retinopathy, nephropathy, and neuropathy in the setting of type 1 diabetes (4,5); in type 2 diabetes, more intensive treatment strategies have likewise been demonstrated to reduce complications (6–8). Intensive glycemic management resulting in lower HbA_{1c} (A1C) levels has also been shown to have a beneficial effect on cardiovascular disease (CVD) complications in type 1 diabetes (9,10); however, the role of intensive diabetes therapy on CVD in type 2 diabetes remains under active investigation (11,12). Some therapies directed at lowering glucose levels have additional benefits with regard to CVD risk factors, while others lower glucose without additional benefits.

The development of new classes of blood glucose–lowering medications to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylureas, and metformin, has increased the treatment options for type 2 diabetes. Whether used alone or in combination with other blood glucose–lowering interventions, the availability of the newer agents has provided an increased number of choices for practitioners and patients and heightened uncertainty regarding the most appropriate means of treating this widespread disease. Although numerous reviews on the management of type 2 diabetes have been published in recent years (13–16), practitioners are often left without a clear pathway of therapy to follow. We developed the following consensus approach to the management of hyperglycemia in the nonpregnant adult to help guide health care providers in choosing the most appropriate interventions for their patients with type 2 diabetes.

Process

The guidelines and algorithm that follow are based on clinical trials that have examined different modalities of therapy of type 2 diabetes and on the authors' clinical experience and judgment, keeping in mind the primary goal of achieving and maintaining glucose levels as close to the

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This document was reviewed and approved by the Professional Practice Committee of the American Diabetes Association and by an ad hoc committee of the European Association for the Study of Diabetes (Ulf Smith, Gothenburg, Sweden; Stefano Del Prato, Pisa, Italy; Clifford Bailey, Birmingham U.K.; and Bernard Charbonnel, Nantes, France).

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Abbreviations: CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; GLP-1, glucagon-like peptide 1; SMBG, self-monitoring of blood glucose; TZD, thiazolidinedione; UKPDS, U.K. Prospective Diabetes Study.

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Table 1—*Summary of antidiabetic interventions as monotherapy*

Interventions	Expected decrease in A1C (%)	Advantages	Disadvantages
Step 1: initial			
Lifestyle to decrease weight and increase activity	1–2	Low cost, many benefits	Fails for most in 1st year
Metformin	1.5	Weight neutral, inexpensive	GI side effects, rare lactic acidosis
Step 2: additional therapy			
Insulin	1.5–2.5	No dose limit, inexpensive, improved lipid profile	Injections, monitoring, hypoglycemia, weight gain
Sulfonylureas	1.5	Inexpensive	Weight gain, hypoglycemia*
TZDs	0.5–1.4	Improved lipid profile	Fluid retention, weight gain, expensive
Other drugs			
α-Glucosidase inhibitors	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Exenatide	0.5–1.0	Weight loss	Injections, frequent GI side effects, expensive, little experience
Glinides	1–1.5†	Short duration	Three times/day dosing, expensive
Pramlintide	0.5–1.0	Weight loss	Injections, three times/day dosing, frequent GI side effects, expensive, little experience

*Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g. chlorpropamide, glyburide [glibenclamide], and sustained-release glipizide) are more likely to cause hypoglycemia than glipizide, glimepiride, and gliclazide. †Repaglinide is more effective at lowering A1C than nateglinide. GI, gastrointestinal.

nondiabetic range as possible. The paucity of high-quality evidence in the form of clinical trials that directly compare different diabetes treatment regimens remains a major impediment to recommending one class of drugs, or a particular combination of therapies, over another. While the algorithm that we propose is likely to engender debate, we hope that the recommendations will help guide the therapy of type 2 diabetes and result in improved glycemic control and health status over time.

Glycemic goals of therapy

Controlled clinical trials, such as the Diabetes Control and Complications Trial (DCCT) (4) and the Stockholm Diabetes Intervention Study (5) in type 1 diabetes and the U.K. Prospective Diabetes Study (UKPDS) (6,7) and Kumamoto Study (8) in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. Although the various clinical trials have had different designs, interventions, and measured outcomes, the trials, in concert with epidemiologic data (17,18), support decreasing glycemia as an effective means of reducing long-term microvascular and neuropathic complications. The most appropriate target levels for blood glucose, on a day-to-day basis, and A1C, as an index of chronic glycemia, have not been systematically studied. However, both the DCCT (4) and the UKPDS (6,7) had as their goals the achievement of glycemic levels in the nondiabetic range. Neither study was able to sustain A1C levels in the nondiabetic range in their intensive-treatment groups, achieving mean levels over time of ~7%, 4 SDs above the nondiabetic mean.

The most recent glycemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complications over time, is "in general" an A1C level <7% (19). For "the individual patient," the A1C should be "as close to normal (<6%) as possible without significant hypoglycemia." The most recent glycemic goal set by the European Union–International Diabetes Federation is an A1C level <6.5%. The upper limit of the nondiabetic range is 6.1% (mean A1C of 5% + 2 SD) with the DCCT-standardized assay, which has been promulgated through the National Glycohemoglobin Standardization Program (NGSP) and adopted by the vast majority of commercially available assays (20). Our consensus is that an A1C of ≥7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level as close to the nondiabetic range as possible or, at a minimum, decreasing the A1C to <7%. We are mindful that this goal is not appropriate or practical for some patients, and clinical judgment, based on the potential benefits and risks of a more intensified regimen, needs to be applied for every patient. Factors such as life expectancy and risk for hypoglycemia need to be considered for every patient before intensifying therapeutic regimens.

Assiduous attention to abnormalities other than hyperglycemia that accompany type 2 diabetes, such as hypertension and dyslipidemia, has been shown to improve microvascular and cardiovascular complications. Readers are referred to published guidelines for a discussion of the rationale and goals of therapy for the nonglycemic risk factors, as well as recommendations as to how to achieve them (1,21,22).

Principles in selecting antihyperglycemic interventions

Choosing specific antihyperglycemic agents is predicated on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, and expense.

Effectiveness in lowering glycemia. Apart from their differential effects on glycemia, there are insufficient data at this time to support a recommendation of one class of glucose-lowering agents, or one combination of medications, over others with regard to effects on complications. In other words, the salutary effects of therapy on long-term complications appear to

be predicated predominantly on the level of glycemic control achieved rather than on any other specific attributes of the intervention(s) used to achieve glycemic goals. The UKPDS compared three classes of glucose-lowering medications (sulfonylurea, metformin, or insulin) but was unable to demonstrate clear superiority of any one drug over the others with regard to complications (6,7). However, the different classes do have variable effectiveness in decreasing glycemic levels (Table 1), and the overarching principle in selecting a particular intervention will be its ability to achieve and maintain glycemic goals. In addition to the intention-to-treat analyses demonstrating the superiority of intensive versus conventional interventions, the DCCT and UKPDS demonstrated a strong correlation between mean A1C levels over time and the development and progression of retinopathy and nephropathy (23,24). Therefore, we think it is reasonable to judge and compare blood glucose–lowering medications, and the combinations of such agents, primarily on the basis of the A1C levels that are achieved and on their specific side effects, tolerability, and expense.

Nonglycemic effects of medications. In addition to variable effects on glycemia, specific effects of individual therapies on CVD risk factors, such as hypertension or dyslipidemia, were also considered important. We also included the effects of interventions that may benefit or worsen the prospects for long-term glycemic control in our recommendations. Examples of these would be changes in body mass, insulin resistance, or insulin secretory capacity in type 2 diabetic patients.

Choosing specific diabetes interventions and their roles in treating type 2 diabetes

Numerous reviews have focused on the characteristics of the specific diabetes interventions listed below (25–33). The aim here is to provide enough information to justify the choices of medications, the order in which they are recommended, and the utility of combinations of therapies. Unfortunately, there is a dearth of high-quality studies that provide head-to-head comparisons of the ability of the medications to achieve the currently recommended glycemic levels. The authors highly recommend that such studies be conducted. However, even in the absence of rigorous, comprehensive studies that directly compare the efficacy of all available glucose-lowering treatments, and their combinations, we feel that there are enough data regarding the characteristics of the individual interventions to provide the guidelines below.

An important intervention that is likely to improve the probability that a patient will have better long-term control of diabetes is to make the diagnosis early, when the metabolic abnormalities of diabetes are usually less severe. Lower levels of glycemia at time of initial therapy are associated with lower A1C over time and decreased long-term complications (34).

Lifestyle interventions. The major environmental factors that increase the risk of type 2 diabetes, presumably in the setting of genetic risk, are overnutrition and a sedentary lifestyle, with consequent overweight and obesity (35). Not surprisingly, interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycemia in established type 2 diabetes (36). While there is still active debate regarding the most beneficial types of diet and exercise, weight loss almost always improves glycemic levels. Unfortunately, the high rate of weight regain has limited the role of lifestyle interventions as an effective means of controlling glycemia long term. The most convincing long-term data that weight loss effectively lowers glycemia have been generated in the follow-up of type 2 diabetic patients who have had bariatric surgery (37,38). In this setting, diabetes is virtually erased, with a mean sustained weight loss of >20 kg (37,38). Studies of the pharmacologic treatment of obesity have been characterized by high drop-out rates, low sustainability, and side effects; weight loss medications cannot be recommended as a primary therapy for diabetes at this time. In addition to the beneficial effects of weight loss on glycemia, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity (37–40). There are few adverse consequences of such lifestyle interventions other than the difficulty in incorporating them into usual lifestyle and sustaining them and the usually minor musculoskeletal injuries and potential problems associated with neuropathy, such as foot trauma and ulcers, that may occur with increased activity. Theoretically, effective weight loss, with its pleiotropic benefits, safety profile, and low cost, should be the most cost-effective means of controlling diabetes, if it could be achieved and maintained long term.

Given these beneficial effects, a lifestyle intervention program to promote weight loss and increase activity levels should, with rare exceptions, be included as part of diabetes management. The beneficial effects of such programs are usually seen rapidly, within weeks to months, and often before there has been substantial weight loss (41). Weight loss of as little as 4 kg will often ameliorate hyperglycemia. However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with type 2 diabetes suggests that a large majority of patients will require the addition of medications over the course of their diabetes.

Medications. The characteristics of currently available antidiabetic interventions, when used as monotherapy, are summarized in Table 1. The glucose-lowering effectiveness of individual therapies and combinations demonstrated in clinical trials is predicated not only on the intrinsic characteristics of the intervention, but also on the baseline glycemia, duration of diabetes, previous therapy, and other factors. A major factor in selecting a class of drugs, or a specific medication within a class, to initiate therapy or when changing therapy, is the ambient level of glycemic control. When levels of glycemia are high (e.g., A1C >8.5%), classes with greater and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy, are recommended; conversely, when glycemic levels are closer to the target levels (e.g., A1C <7.5%), medications with lesser potential to lower glycemia and/or a slower onset of action may be considered. Obviously, the choice of glycemic goals and the medications used to achieve them must be individualized for each patient, balancing the potential for lowering A1C and anticipated long-term benefit with specific safety issues, as well as other characteristics of regimens, including side effects, tolerability, patient burden and long-term adherence, expense, and the nonglycemic effects of the medications. Finally, type 2 diabetes is a progressive disease with worsening glycemia over time. Therefore, addition of medications is the rule, not the exception, if treatment goals are to be met over time.

Metformin. Metformin is the only biguanide available in most of the world. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typi-

cally, metformin monotherapy will lower A1C by ~1.5 percentage points (27,42). It is generally well tolerated, with the most common adverse effects being gastrointestinal. Although always a matter of concern because of its potentially fatal outcome, lactic acidosis is quite rare (<1 case per 100,000 treated patients) (43). Metformin monotherapy is usually not accompanied by hypoglycemia and has been used safely, without causing hypoglycemia, in patients with pre-diabetic hyperglycemia (44). The major nonglycemic effect of metformin is either weight stability or modest weight loss, in contrast to many of the other blood glucose–lowering medications. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes that needs to be confirmed (7).

Sulfonylureas. Sulfonylureas lower glycemia by enhancing insulin secretion. They appear to have an effect similar to metformin, and they lower A1C by ~1.5 percentage points (26). The major adverse side effect is hypoglycemia, but severe episodes, characterized by need for assistance, coma, or seizure, are infrequent. However, such episodes are more frequent in the elderly. Episodes can be both prolonged and life threatening, although these are very rare. Several of the newer sulfonylureas have a relatively lower risk for hypoglycemia (Table 1) (45,46). In addition, weight gain of ~2 kg is common with the initiation of sulfonylurea therapy. This may have an adverse impact on CVD risk, although it has not been established. Finally, sulfonylurea therapy was implicated as a potential cause of increased CVD mortality in the University Group Diabetes Program (47). Concerns raised by the University Group Diabetes Program study that sulfonylurea therapy may increase CVD mortality in type 2 diabetes were not substantiated by the UKPDS (6).

Glinides. Like the sulfonylureas, the glinides stimulate insulin secretion, although they bind to a different site within the sulfonylurea receptor (28). They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. Of the two glinides currently available in the U.S., repaglinide is almost as effective as metformin or the sulfonylureas, decreasing A1C by ~1.5 percentage points. Nateglinide is somewhat less effective in lowering A1C than repaglinide when used as monotherapy or in combination therapy (48,49). The glinides have a similar risk for weight gain as the sulfonylureas, but hypoglycemia may be less frequent, at least with nateglinide, than with some sulfonylureas (49,50).

α-Glucosidase inhibitors. α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering postprandial glucose levels without causing hypoglycemia. They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing A1C by 0.5–0.8 percentage points (29). Since carbohydrate is absorbed more distally, malabsorption and weight loss do not occur; however, increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms. This side effect has led to discontinuation of the α-glucosidase inhibitors by 25–45% of participants in clinical trials (29,51). One clinical trial examining acarbose as a means of preventing the development of diabetes in high-risk subjects with impaired glucose tolerance showed an unexpected reduction in severe CVD outcomes (51). This potential benefit of α-glucosidase inhibitors needs to be confirmed.

Thiazolidinediones. Thiazolidinediones (TZDs or glitazones) are peroxisome proliferator–activated receptor γ modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers") (31). The limited data regarding the blood glucose–lowering effectiveness of TZDs when used as monotherapy have demonstrated a 0.5–1.4% decrease in A1C. The most common adverse effects with TZDs are weight gain and fluid retention. There is an increase in adiposity, largely subcutaneous, with redistribution of fat from visceral deposits shown in some studies. The fluid retention usually manifests as peripheral edema, though new or worsened heart failure can occur. The TZDs either have a beneficial or neutral effect on atherogenic lipid profiles, with pioglitazone having a more beneficial effect than rosiglitazone (52,53). The PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) study demonstrated no significant effects of pioglitazone compared with placebo on the primary CVD outcome (composite of all-cause mortality, nonfatal and silent myocardial infarction, stroke, major leg amputation, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention, and leg revascularization) after 3 years of follow-up, but a 16% reduction in death, myocardial infarction, and stroke, a secondary end point, was reported with marginal statistical significance (54).

Insulin. Insulin is the oldest of the currently available medications and has the most clinical experience. Although initially developed to treat the insulin-deficient type 1 diabetic patient, in whom it is life saving, insulin was used early on to treat the insulin-resistant form of diabetes recognized by Himsworth and Kerr (55). Insulin is the most effective of diabetes medications in lowering glycemia. It can, when used in adequate doses, decrease any level of elevated A1C to, or close to, the therapeutic goal. Unlike the other blood glucose–lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Relatively large doses of insulin (≥1 unit/kg), compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance of type 2 diabetes and lower A1C to goal. Although initial therapy is aimed at increasing basal insulin supply, usually with intermediate- or long-acting insulins, patients may also require prandial therapy with short- or rapid-acting insulins as well (Fig. 1). Insulin therapy has beneficial effects on triglyceride and HDL cholesterol levels (56) but is associated with weight gain of ~2–4 kg, probably proportional to the correction of glycemia and owing predominantly to the reduction of glycosuria. As with sulfonylurea therapy, the weight gain may have an adverse effect on cardiovascular risk. Insulin therapy is also associated with hypoglycemia, albeit much less frequently than in type 1 diabetes. In clinical trials aimed at normoglycemia and achieving a mean A1C of ~7%, severe hypoglycemic episodes (defined as requiring help from another person to treat) occurred at a rate of between 1 and 3 per 100 patient-years (8,56–59) compared with 61 per 100 patient-years in the DCCT intensive-therapy group (4). Insulin analogs with longer, nonpeaking profiles may decrease the risk of hypoglycemia compared with NPH, and analogs with very short durations of action may reduce the risk of hypoglycemia compared with regular insulin (60,61). Inhaled insulin was approved in the U.S. in 2006 for the treatment of type 2 diabetes. Published clinical studies to date have not demonstrated whether inhaled insulin, given as monotherapy (62,63) or in combination with an injection of long-acting insulin (64), can lower A1C to ≤7%.

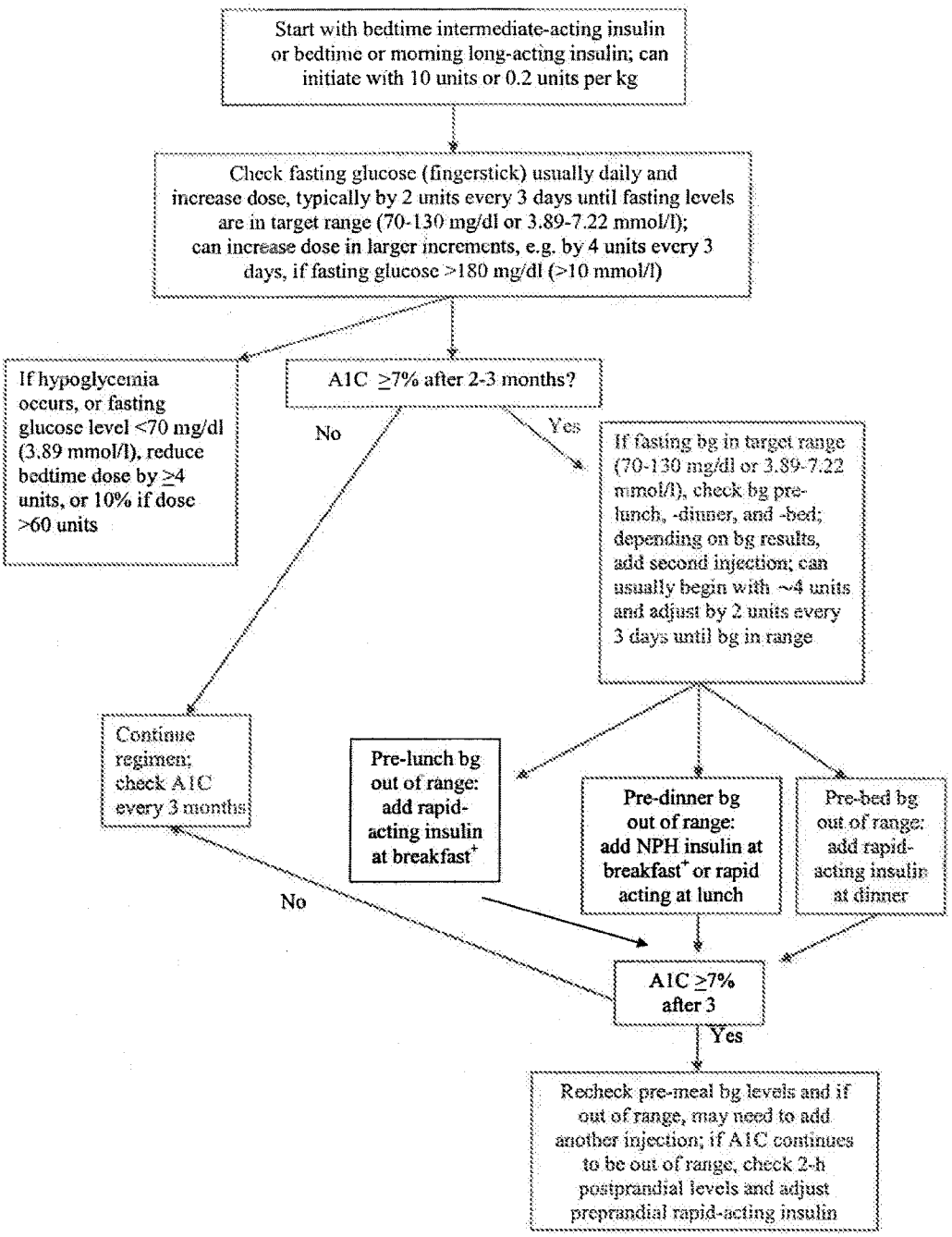

Figure 1—*Initiation and adjustment of insulin regimens. Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin. See ref. 71 for more detailed instructions. +Premixed insulins are not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast and/or dinner if proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available. bg, blood glucose.*

Glucagon-like peptide 1 agonists (exenatide). Glucagon-like peptide 1 (GLP-1) 7-37, a naturally occurring peptide produced by the L-cells of the small intestine, stimulates insulin secretion. Exendin-4 has homology with the human GLP-1 sequence but has a longer circulating half-life. It binds avidly to the GLP-1 receptor on the pancreatic β-cell and potentiates glucose-mediated insulin secretion (32). Synthetic exendin-4 (exenatide) was approved for use in the U.S. in 2005 and is administered twice per day by subcutaneous injection. Although there are far less published data on this new compound than the other blood glucose–lowering medications, exendin-4 appears to lower A1C by 0.5–1 percentage points, mainly by lowering postprandial blood glucose levels (65–68). Exenatide also suppresses glucagon secretion and slows gastric motility. It is not associated with hypoglycemia but has a relatively high frequency of gastrointestinal side effects, with 30–45% of treated patients experiencing one or more episodes of nausea, vomiting, or diarrhea

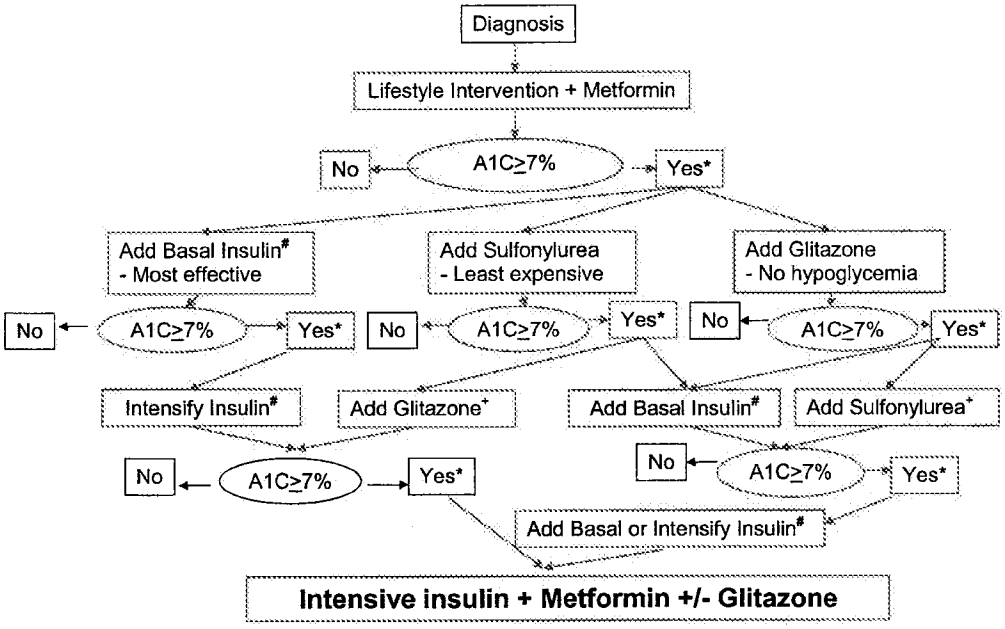

Figure 2—*Algorithm for the metabolic management of type 2 diabetes. Reinforce lifestyle intervention at every visit. *Check A1C every 3 months until <7% and then at least every 6 months. +Although three oral agents can be used, initiation and intensification of insulin therapy is preferred based on effectiveness and expense. #See Fig. 1 for initiation and adjustment of insulin.*

(65–68). In published trials, exenatide is associated with an ~2- to 3-kg weight loss over 6 months, some of which may be a result of its gastrointestinal side effects. Currently, exenatide is approved for use in the U.S. with sulfonylurea and/or metformin.

Amylin agonists (pramlintide). Pramlintide is a synthetic analog of the β-cell hormone amylin. Currently, pramlintide is approved for use in the U.S. only as adjunctive therapy with insulin.

Pramlintide is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion, and predominantly decreases postprandial glucose excursions (33). In clinical studies, A1C has been decreased by 0.5–0.7 percentage points (69). The major clinical side effects of this drug, which is injected before meals, are gastrointestinal in nature. Approximately 30% of treated participants in the clinical trials have developed nausea. Weight loss associated with this medication is ~1–1.5 kg over 6 months; as with exenatide, some of the weight loss may be the result of gastrointestinal side effects.

How to initiate diabetes therapy and advance interventions

Except in rare circumstances, such as patients who are extremely catabolic or hyperosmolar, who are unable to hydrate themselves adequately, or with diabetic ketoacidosis (see SPECIAL CONSIDERATIONS/PATIENTS below), hospitalization is not required to initiate or adjust therapy. The patient is the key player in the diabetes care team and should be trained and empowered to prevent and treat hypoglycemia, as well as to adjust medications with the guidance of health care providers to achieve glycemic goals. Many patients may be managed effectively with monotherapy; however, the progressive nature of the disease will require the use of combination therapy in many, if not most, patients over time to achieve and maintain glycemia in the target range.

The measures of glycemia that are initially targeted on a day-to-day basis are the fasting and preprandial glucose levels. Self-monitoring of blood glucose (SMBG) is an important element in adjusting or adding new interventions and, in particular, in titrating insulin doses. The need for and number of required SMBG measurements are not clear (70) but are dependent on the medications used. Oral hypoglycemic regimens that do not include sulfonylureas, and are therefore not likely to cause hypoglycemia, usually do not require SMBG. However, SMBG may be used to determine whether therapeutic blood glucose targets are being achieved and to adjust treatment regimens without requiring the patient to have laboratory-based blood glucose testing. A fasting glucose level measured several times per week generally correlates well with the A1C level. Insulin therapy requires more frequent monitoring.

The levels of plasma or capillary glucose (most meters that measure fingerstick capillary samples are adjusted to provide values equivalent to plasma glucose) that should result in long-term glycemia in the nondiabetic target range, as measured by A1C, are fasting and preprandial levels between 70 and 130 mg/dl (3.89 and 7.22 mmol/l). If these levels are not consistently achieved, or A1C remains above the desired target, postprandial levels, usually measured 90–120 min after a meal, may be checked. They should be less than 180 mg/dl (10 mmol/l) to achieve A1C levels in the target range.

Attempts to achieve target glycemic levels with regimens including sulfonylureas or insulin may be associated with modest hypoglycemia, with glucose levels in the 55- to 70-mg/dl (3.06- to 3.89-mmol) range. These episodes are generally well tolerated, easily treated with oral carbohydrate, such as glucose tablets or 4–6 oz (120–180 ml) juice or nondiet soda, and rarely progress to more severe hypoglycemia, including loss of consciousness or seizures.

Algorithm

The algorithm (Fig. 2) takes into account the characteristics of the individual interventions, their synergies, and expense. The goal is to achieve and maintain glycemic levels as close to the nondiabetic range as possible and to change interventions at as rapid a pace as titration of medications allows. Pramlintide, exenatide, α-glucosidase inhibitors, and the glinides are not included in this algorithm, owing

Table 2—*Titration of metformin*

1) Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner).
2) After 5–7 days, if GI side effects have not occurred, advance dose to 850 or 1,000 mg before breakfast and dinner.
3) If GI side effects appear as doses advanced, can decrease to previous lower dose and try to advance dose at a later time.
4) The maximum effective dose is usually 850 mg twice per day, with modestly greater effectiveness with doses up to 3 g per day. GI side effects may limit the dose that can be used.
5) Based on cost considerations, generic metformin is the first choice of therapy. A longer-acting formulation is available in some countries and can be given once per day.

GI, gastrointestinal.

to their generally lower overall glucose-lowering effectiveness, limited clinical data, and/or relative expense (Table 1). However, they may be appropriate choices in selected patients.

Step 1: lifestyle intervention and metformin. Based on the numerous demonstrated short- and long-term benefits that accrue when weight loss and increased levels of activity are achieved and maintained, and the cost-effectiveness of lifestyle interventions when they succeed, the consensus is that lifestyle interventions should be initiated as the first step in treating new-onset type 2 diabetes (Fig. 2). These interventions should be implemented by health care professionals with appropriate training, usually registered dietitians with training in behavioral modification, and be sensitive to ethnic and cultural differences among populations. Moreover, lifestyle interventions to improve glucose, blood pressure, and lipids levels and to promote weight loss or at least avoid weight gain should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used. For the 10–20% of patients with type 2 diabetes who are not obese or overweight, modification of dietary composition and activity levels may play a supporting role, but medications are generally required earlier (see SPECIAL CONSIDERATIONS/PATIENTS below).

The authors recognize that for most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain metabolic goals, either because of failure to lose weight, weight regain, progressive disease or a combination of factors. Therefore, our consensus is that metformin therapy should be initiated concurrent with lifestyle intervention at diagnosis. Metformin is recommended as the initial pharmacologic therapy, in the absence of specific contraindications, for its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost. Metformin treatment should be titrated to its maximally effective dose over 1–2 months, as tolerated (Table 2). Rapid addition of other glucose-lowering medications should be considered in the setting of persistent symptomatic hyperglycemia.

Step 2: additional medications. If lifestyle intervention and maximal tolerated dose of metformin fail to achieve or sustain glycemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when A1C goal is not achieved. There was no strong consensus regarding the second medication added after metformin other than to choose among insulin, a sulfonylurea, or a TZD (Fig. 2). As discussed above, the A1C level will determine in part which agent is selected next, with consideration given to the more effective glycemia-lowering agent, insulin, for patients with A1C >8.5% or with symptoms secondary to hyperglycemia. Insulin can be initiated with a basal (intermediate- or long-acting) insulin (see Fig. 1 for suggested initial insulin regimens) (71). The relative increased cost of the newer agents that are only available as brand medications must be balanced against their relative benefits.

Step 3: further adjustments. If lifestyle, metformin, and a second medication do not result in goal glycemia, the next step should be to start, or intensify, insulin therapy (Fig. 1). When A1C is close to goal (<8.0%), addition of a third oral agent could be considered; however, this approach is relatively more costly and potentially not as effective in lowering glycemia compared with adding or intensifying insulin (72). Intensification of insulin therapy usually consists of additional injections that might include a short- or rapid-acting insulin given before selected meals to reduce postprandial glucose excursions (Fig. 1). When prandial rapid- or very-rapid-acting insulin injections are started, insulin secretagogues (sulfonylurea or glinides) should be discontinued, or tapered and then discontinued, since they are not considered synergistic with administered insulin.

Rationale in selecting specific combinations

More than one medication will be necessary for the majority of patients over time. Selection of the individual agents should be made on the basis of their glucose-lowering effectiveness and other characteristics listed in Table 1. However, when adding second and potentially third antihyperglycemic medications, the synergy of particular combinations and other interactions should be considered. In general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. Insulin plus metformin (73) and insulin plus a TZD (74) are particularly effective means of lowering glycemia. The increased risk of fluid retention with the latter combination must be considered. (TZD in combination with insulin is not currently approved in the European Union.) Although both TZDs and metformin effectively increase sensitivity to insulin, they have different target organs and have been shown to have modest additive effects, with addition of TZD to metformin lowering A1C by 0.3–0.8% (75,76).

Special considerations/patients

In the setting of severely uncontrolled diabetes with catabolism, defined as fasting plasma glucose levels >250 mg/dl (13.9 mmol/l), random glucose levels consistently >300 mg/dl (16.7 mmol/l), A1C >10%, or the presence of ketonuria, or as symptomatic diabetes with polyuria, polydipsia, and weight loss, insulin therapy in combination with lifestyle intervention is the treatment of choice. Some patients with these characteristics will have unrecognized type 1 diabetes; others will have type 2 diabetes but with severe insulin deficiency. Insulin can be titrated rapidly and is associated with the greatest likelihood of returning glucose levels rapidly to target levels. After symptoms are relieved, oral agents can often be added and it may be possible to withdraw insulin, if preferred.

Conclusions/summary

Type 2 diabetes is epidemic. Its long-term consequences translate into enormous human suffering and economic costs. We now understand that much of the morbidity associated with long-term complications can be substantially reduced with interventions that achieve glucose levels

close to the nondiabetic range. Although new classes of medications, and numerous combinations, have been demonstrated to lower glycemia, current-day management has failed to achieve and maintain the glycemic levels most likely to provide optimal health care status for people with diabetes.

The guidelines and treatment algorithm presented here emphasize

- achievement and maintenance of normal glycemic goals;
- initial therapy with lifestyle intervention and metformin;
- rapid addition of medications, and transition to new regimens, when target glycemic goals are not achieved or sustained; and
- early addition of insulin therapy in patients who do not meet target goals.

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Exhibit 3

Medical Management of Hyperglycemia in Type 2 Diabetes: A Consensus Algorithm for the Initiation and Adjustment of Therapy

A consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes

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The consensus algorithm for the medical management of type 2 diabetes was published in August 2006 with the expectation that it would be updated, based on the availability of new interventions and new evidence to establish their clinical role. The authors continue to endorse the principles used to develop the algorithm and its major features. We are sensitive to the risks of changing the algorithm cavalierly or too frequently, without compelling new information. An update to the consensus algorithm published in January 2008 specifically addressed safety issues surrounding the thiazolidinediones. In this revision, we focus on the new classes of medications that now have more clinical data and experience.

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The epidemic of type 2 diabetes and the recognition that achieving specific glycemic goals can substantially reduce morbidity have made the effective treatment of hyperglycemia a top priority (1–3). While the management of hyperglycemia, the hallmark metabolic abnormality associated with type 2 diabetes, has historically taken center stage in the treatment of diabetes, therapies directed at other coincident features, such as dyslipidemia, hypertension, hypercoagulability, obesity, and insulin resistance, have also been a major focus of research and therapy. Maintaining glycemic levels as close to the nondiabetic range as possible has been demonstrated to have a powerful beneficial effect on diabetes-specific microvascular complications, including retinopathy, nephropathy, and neuropathy, in the setting of type 1 diabetes (4,5); in type 2 diabetes, more intensive treatment strategies have likewise been demonstrated to reduce microvascular complications (6–8). Intensive glycemic management resulting in lower A1C levels has also been shown to have a beneficial effect on cardiovascular disease (CVD) complications in type 1 diabetes (9,10); however, current studies have failed to demonstrate a beneficial effect of intensive diabetes therapy on CVD in type 2 diabetes (11–13).

The development of new classes of blood glucose–lowering medications to supplement the older therapies, such as lifestyle-directed interventions, insulin, sulfonylureas, and metformin, has increased the number of treatment options available for type 2 diabetes. Whether used alone or in combination with other blood glucose–lowering interventions, the increased number of choices available to practitioners and patients has heightened uncertainty regarding the most appropriate means of treating this widespread disease (14). Although numerous reviews on the management of type 2 diabetes have been published in recent years (15–17), practitioners are often left without a clear pathway of therapy to follow. We developed the following consensus approach to the management of hyperglycemia in the nonpregnant adult to help guide health care providers in choosing the most appropriate interventions for their patients with type 2 diabetes.

Process

The guidelines and algorithm that follow are derived from two sources. One source is the clinical trials that address the effectiveness and safety of the different modalities of therapy. Here, the writing group reviewed a wide variety of studies related to the use of drugs as monotherapy or in combination to lower glycemia. Unfortunately, the paucity of high-quality evidence in the form of well-controlled clinical trials that directly compare different diabetes treatment regimens remains a major impediment to recommending one class of drugs, or a particular combination of therapies, over another.

The second source of material that informed our recommendations was clinical judgement, that is, our collective knowledge and clinical experience, which takes into account benefits, risks, and costs in the treatment of diabetes. As in all clinical decision making, an evidence-based review of

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the literature must also be supplemented by value judgements, where the benefits of treatment are weighed against risks and costs in a subjective fashion. While we realize that others may have different judgements, we believe that the recommendations made in this new iteration of our treatment algorithm will guide therapy and result in improved glycemic control and health status over time.

Glycemic goals of therapy

Controlled clinical trials, such as the Diabetes Control and Complications Trial (DCCT) (4) and the Stockholm Diabetes Study in type 1 diabetes (5) and the UK Prospective Diabetes Study (UKPDS) (6,7) and Kumamoto study (8) in type 2 diabetes, have helped to establish the glycemic goals of therapy that result in improved long-term outcomes. The clinical trials, in concert with epidemiological data (18,19), support decreasing glycemia as an effective means of reducing long-term microvascular and neuropathic complications. The most appropriate target levels for blood glucose, on a day-to-day basis, and A1C, as an index of chronic glycemia, have not been systematically studied. However, both the DCCT (4) and the UKPDS (6,7) had as their goals the achievement of glycemic levels in the nondiabetic range. Neither study was able to maintain A1C levels in the nondiabetic range in their intensive treatment groups, achieving mean levels over time of ~7%, which is 4 SDs above the nondiabetic mean.

The most recent glycemic goal recommended by the American Diabetes Association, selected on the basis of practicality and the projected reduction in complications over time, is, in general, an A1C level of <7% (1). The most recent glycemic goal set by the International Diabetes Federation is an A1C level of <6.5%. The upper limit of the nondiabetic range is 6.1% (mean ± SD. A1C level of 5 ± 2%) with the DCCT/UKPDS-standardized assay, which has been promulgated through the National Glycohemoglobin Standardization Program (NGSP) and adopted by the vast majority of commercially available assays (20). Several recent clinical trials have aimed for A1C levels ≤6.5% with a variety of interventions (11,12). The results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, which had the primary objective of decreasing CVD with interventions aimed at achieving an A1C level of <6.0% vs. interventions aimed at achieving an A1C level of <7.9%, showed excess CVD mortality in the intensive treatment group (11). Results from the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial and the Veterans Affairs Diabetes Trial, both of which had different interventions and study populations than ACCORD, did not demonstrate any excess total or CVD mortality with intensive regimens that achieved A1C levels comparable with the 6.5% in ACCORD (12,13). However, none of the studies has demonstrated a benefit of intensive glycemic control on their primary CVD outcomes. Our consensus is that an A1C level of ≥7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level of <7%. We are mindful that this goal is not appropriate or practical for some patients, and clinical judgement based on the potential benefits and risks of a more intensified regimen needs to be applied for every patient. Factors such as life expectancy, risk of hypoglycemia, and the presence of CVD need to be considered for every patient before intensifying the therapeutic regimen.

Assiduous attention to abnormalities other than hyperglycemia that accompany type 2 diabetes, such as hypertension and dyslipidaemia, has been shown to improve microvascular and cardiovascular complications. Readers are referred to published guidelines for a discussion of the rationale and goals of therapy for the nonglycemic risk factors, as well as recommendations on how to achieve them (1,21,22).

Principles in selecting antihyperglycemic interventions

Our choice of specific antihyperglycemic agents is predicated on their effectiveness in lowering glucose, extraglycemic effects that may reduce long-term complications, safety profiles, tolerability, ease of use, and expense.

Effectiveness in lowering glycaemia

Except for their differential effects on glycemia, there are insufficient data at this time to support a recommendation of one class of glucose-lowering agents, or one combination of medications, over others with regard to effects on complications. In other words, the salutary effects of therapy on long-term complications appear to be predicated predominantly on the level of glycemic control achieved rather than on any other specific attributes of the intervention(s) used to achieve glycemic goals. The UKPDS compared three classes of glucose-lowering medications (sulfonylurea, metformin, or insulin) but was unable to demonstrate clear superiority of any one drug over the others with regard to diabetes complications (6,7). However, the different classes do have variable effectiveness in decreasing glycemic levels (Table 1), and the overarching principle in selecting a particular intervention will be its ability to achieve and maintain glycemic goals. In addition to their intention-to-treat analyses demonstrating the superiority of intensive versus conventional interventions, the DCCT and UKPDS demonstrated a strong correlation between mean A1C levels over time and the development and progression of retinopathy and nephropathy (23,24). Therefore, we think it is reasonable to judge and compare blood glucose–lowering medications, as well as combinations of such agents, primarily on the basis of their capacity to decrease and maintain A1C levels and according to their safety, specific side effects, tolerability, ease of use, and expense.

Nonglycemic effects of medications

In addition to variable effects on glycemia, specific effects of individual therapies on CVD risk factors, such as hypertension or dyslipidemia, were also considered important. We also included the effects of interventions that may benefit or worsen the prospects for long-term glycemic control in our recommendations. Examples of these would be changes in body mass, insulin resistance, or insulin secretory capacity in type 2 diabetic patients.

Choosing specific diabetes interventions and their roles in treating type 2 diabetes

Numerous reviews have focused on the characteristics of the specific diabetes interventions listed below (25–34). In addition, meta-analyses and reviews have summarized and compared the glucose-lowering effectiveness and other characteristics of the medications (35–37). The aim here is to provide enough information to justify the choices of medications, the order in which they are recommended, and the use of combinations of therapies. Unfortunately, there is a dearth of high-quality studies that provide head-to-head comparisons of the ability of the medications to achieve the currently recommended glycemic levels. The authors

Table 1—*Summary of glucose-lowering interventions*

Intervention	Expected decrease in A1C with monotherapy (%)	Advantages	Disadvantages
Tier 1: well-validated core			
Step 1: initial therapy			
Lifestyle to decrease weight and increase activity	1.0–2.0	Broad benefits	Insufficient for most within first year
Metformin	1.0–2.0	Weight neutral	GI side effects, contraindicated with renal insufficiency
Step 2: additional therapy			
Insulin	1.5–3.5	No dose limit, rapidly effective, improved lipid profile	One to four injections daily, monitoring, weight gain, hypoglycemia, analogues are expensive
Sulfonylurea	1.0–2.0	Rapidly effective	Weight gain, hypoglycemia (especially with glibenclamide or chlorpropamide)
Tier 2: less well validated			
TZDs	0.5–1.4	Improved lipid profile (pioglitazone), potential decrease in MI (pioglitazone)	Fluid retention, CHF, weight gain, bone fractures, expensive, potential increase in MI (rosiglitazone)
GLP-1 agonist	0.5–1.0	Weight loss	Two injections daily, frequent GI side effects, long-term safety not established, expensive
Other therapy			
α-Glucosidase inhibitor	0.5–0.8	Weight neutral	Frequent GI side effects, three times/day dosing, expensive
Glinide	0.5–1.5[a]	Rapidly effective	Weight gain, three times/day dosing, hypoglycemia, expensive
Pramlintide	0.5–1.0	Weight loss	Three injections daily, frequent GI side effects, long-term safety not established, expensive
DPP-4 inhibitor	0.5–0.8	Weight neutral	Long-term safety not established, expensive

[a]Repaglinide more effective in lowering A1C than nateglinide. CHF, congestive heart failure; GI, gastrointestinal; MI, myocardial infarction.

highly recommend that such studies be conducted. However, even in the absence of rigorous, comprehensive studies that directly compare the efficacy of all available glucose-lowering treatments and their combinations, we feel that there are enough data regarding the characteristics of the individual interventions to provide the guidelines below.

An important intervention that is likely to improve the probability that a patient will have better long-term control of diabetes is to make the diagnosis early, when the metabolic abnormalities of diabetes are usually less severe. Lower levels of glycemia at the time of initial therapy are associated with lower A1C levels over time and decreased long-term complications (38).

Lifestyle interventions

The major environmental factors that increase the risk of type 2 diabetes are overnutrition and a sedentary lifestyle, with consequent overweight and obesity (39,40). Not surprisingly, interventions that reverse or improve these factors have been demonstrated to have a beneficial effect on control of glycemia in established type 2 diabetes (41). Unfortunately, the high rate of weight regain has limited the role of lifestyle interventions as an effective means of controlling glycemia in the long term. The most convincing long-term data indicating that weight loss effectively lowers glycemia have been generated in the follow-up of type 2 diabetic patients who have had bariatric surgery. In this setting, with a mean sustained weight loss of >20 kg, diabetes is virtually eliminated (42–45). In addition to the beneficial effects of weight loss on glycemia, weight loss and exercise improve coincident CVD risk factors, such as blood pressure and atherogenic lipid profiles, and ameliorate other consequences of obesity (41,46,47). There are few adverse consequences of such life-

style interventions other than difficulty in incorporating them into usual lifestyle and sustaining them and the usually minor musculoskeletal injuries and potential problems associated with neuropathy, such as foot trauma and ulcers, that may occur as a result of increased activity. Theoretically, effective weight loss, with its pleiotropic benefits, safety profile, and low cost, should be the most cost-effective means of controlling diabetes—if it could be achieved and maintained over the long term.

Given these beneficial effects, which are usually seen rapidly—within weeks to months—and often before there has been substantial weight loss (47), a lifestyle intervention program to promote weight loss and increase activity levels should, with rare exceptions, be included as part of diabetes management. Weight loss of as little as 4 kg will often ameliorate hyperglycemia. However, the limited long-term success of lifestyle programs to maintain glycemic goals in patients with type 2 diabetes suggests that the large majority of patients will require the addition of medications over the course of their diabetes.

Medications

The characteristics of currently available glucose-lowering interventions, when used as monotherapy, are summarized in Table 1. The glucose-lowering effectiveness of individual therapies and combinations demonstrated in clinical trials is predicated not only on the intrinsic characteristics of the intervention but also on the duration of diabetes, baseline glycemia, previous therapy, and other factors. A major factor in selecting a class of drugs, or a specific medication within a class, to initiate therapy or when changing therapy, is the ambient level of glycemic control. When levels of glycemia are high (e.g., A1C >8.5%), classes with greater and more rapid glucose-lowering effectiveness, or potentially earlier initiation of combination therapy, are recommended; however, patients with recent-onset diabetes often respond adequately to less intensive interventions than those with longer-term disease (48). When glycemic levels are closer to the target levels (e.g., A1C <7.5%), medications with lesser potential to lower glycemia and/or a slower onset of action may be considered.

Obviously, the choice of glycemic goals and the medications used to achieve them must be individualized for each patient, balancing the potential for lowering A1C and anticipated long-term benefit with specific safety issues, as well as other characteristics of regimens, including side effects, tolerability, ease of use, long-term adherence, expense, and the nonglycemic effects of the medications. Type 2 diabetes is a progressive disease characterized by worsening glycemia; higher doses and additional medications are required over time if treatment goals are to be met.

Metformin. In most of the world, metformin is the only biguanide available. Its major effect is to decrease hepatic glucose output and lower fasting glycemia. Typically, metformin monotherapy will lower A1C levels by ~1.5 percentage points (27,49). It is generally well tolerated, with the most common adverse effects being gastrointestinal. Metformin monotherapy is not usually accompanied by hypoglycemia and has been used safely, without causing hypoglycemia, in patients with prediabetic hyperglycemia (50). Metformin interferes with vitamin B_{12} absorption but is very rarely associated with anemia (27). The major nonglycemic effect of metformin is either weight stability or modest weight loss, in contrast with many of the other blood glucose–lowering medications. The UKPDS demonstrated a beneficial effect of metformin therapy on CVD outcomes (7), which needs to be confirmed. Renal dysfunction is considered a contraindication to metformin use because it may increase the risk of lactic acidosis, an extremely rare (less than 1 case per 100,000 treated patients) but potentially fatal complication (51). However, recent studies have suggested that metformin is safe unless the estimated glomerular filtration rate falls to <30 ml/min (52).

Sulfonylureas. Sulfonylureas lower glycemia by enhancing insulin secretion. In terms of efficacy, they appear to be similar to metformin, lowering A1C levels by ~1.5 percentage points (26,49). The major adverse side effect is hypoglycemia, which can be prolonged and life threatening, but such episodes, characterized by a need for assistance, coma, or seizure, are infrequent. However, severe episodes are relatively more frequent in the elderly. Chlorpropamide and glibenclamide (known as glyburide in the U.S. and Canada), are associated with a substantially greater risk of hypoglycemia than other second-generation sulfonylureas (gliclazide, glimepiride, glipizide, and their extended formulations), which are preferable (Table 1) (53,54). In addition, weight gain of ~2 kg is common following the initiation of sulfonylurea therapy. Although the onset of the glucose-lowering effect of sulfonylurea monotherapy is relatively rapid compared with, for example, the thiazolidinediones (TZDs), maintenance of glycemic targets over time is not as good as monotherapy with a TZD or metformin (55). Sulfonylurea therapy was implicated as a potential cause of increased CVD mortality in the University Group Diabetes Program (UGDP) study (56). Concerns raised by the UGDP that sulfonylureas, as a drug class, may increase CVD mortality in type 2 diabetes were not substantiated by the UKPDS or ADVANCE study (6,12). The glycemic benefits of sulfonylureas are nearly fully realized at half-maximal doses, and higher doses should generally be avoided.

Glinides. Like the sulfonylureas, the glinides stimulate insulin secretion, although they bind to a different site within the sulfonylurea receptor (28). They have a shorter circulating half-life than the sulfonylureas and must be administered more frequently. Of the two glinides currently available in the U.S., repaglinide is almost as effective as metformin or the sulfonylureas, decreasing A1C levels by ~1.5 percentage points. Nateglinide is somewhat less effective in lowering A1C than repaglinide when used as monotherapy or in combination therapy (57,58). The risk of weight gain is similar to that for the sulfonylureas, but hypoglycemia may be less frequent, at least with nateglinide, than with some sulfonylureas (58,59).

α-Glucosidase inhibitors. α-Glucosidase inhibitors reduce the rate of digestion of polysaccharides in the proximal small intestine, primarily lowering postprandial glucose levels without causing hypoglycemia. They are less effective in lowering glycemia than metformin or the sulfonylureas, reducing A1C levels by 0.5–0.8 percentage points (29). Since carbohydrate is absorbed more distally, malabsorption and weight loss do not occur; however, increased delivery of carbohydrate to the colon commonly results in increased gas production and gastrointestinal symptoms. In clinical trials, 25–45% of participants have discontinued α-glucosidase inhibitor use as a result of this side effect (29,60).

One clinical trial examining acarbose as a means of preventing the development of diabetes in high-risk individuals with impaired glucose tolerance showed an unexpected reduction in severe CVD outcomes

(60). This potential benefit of α-glucosidase inhibitors needs to be confirmed.

Thiazolidinediones. Thiazolidinediones (TZDs or glitazones) are peroxisome proliferator–activated receptor γ modulators; they increase the sensitivity of muscle, fat, and liver to endogenous and exogenous insulin ("insulin sensitizers") (31). The data regarding the blood glucose–lowering effectiveness of TZDs when used as monotherapy have demonstrated a 0.5–1.4 percentage point decrease in A1C. The TZDs appear to have a more durable effect on glycemic control, particularly compared with sulfonylureas (55). The most common adverse effects with TZDs are weight gain and fluid retention, with peripheral edema and a twofold increased risk for congestive heart failure (61,62). There is an increase in adiposity, largely subcutaneous, with some reduction in visceral fat shown in some studies. The TZDs either have a beneficial (pioglitazone) or neutral (rosiglitazone) effect on atherogenic lipid profiles (63,64). Several meta-analyses have suggested a 30–40% relative increase in risk for myocardial infarction (65,66) with rosiglitazone. On the other hand, the Prospective Pioglitazone Clinical Trial in macrovascular events (PROactive) demonstrated no significant effects of pioglitazone compared with placebo on the primary CVD outcome (a composite of all-cause mortality, nonfatal and silent myocardial infarction, stroke, major leg amputation, acute coronary syndrome, coronary artery bypass graft or percutaneous coronary intervention, and leg revascularization) after 3 years of follow-up (67). Pioglitazone was associated with a 16% reduction in death, myocardial infarction, and stroke—a controversial secondary end point reported to have marginal statistical significance (67). Meta-analyses have supported a possible beneficial effect of pioglitazone on CVD risk (68). Although the data are less than conclusive for a CVD risk with rosiglitazone or a CVD benefit with pioglitazone, we have previously advised (69) caution in using either TZD on the basis that they are both associated with increased risks of fluid retention and congestive heart failure and an increased incidence of fractures in women and perhaps in men (55,61,62,70). Although the meta-analyses discussed above are not conclusive regarding the potential cardiovascular risk associated with rosiglitazone, given that other options are now recommended, the consensus group members unanimously advised against using rosiglitazone. Currently, in the U.S., the TZDs are approved for use in combination with metformin, sulfonylureas, glinides, and insulin.

Insulin. Insulin is the oldest of the currently available medications and, therefore, the treatment with which we have the most clinical experience. It is also the most effective at lowering glycemia. Insulin can, when used in adequate doses, decrease any level of elevated A1C to, or close to, the therapeutic goal. Unlike the other blood glucose–lowering medications, there is no maximum dose of insulin beyond which a therapeutic effect will not occur. Relatively large doses of insulin (≥1 unit/kg), compared with those required to treat type 1 diabetes, may be necessary to overcome the insulin resistance of type 2 diabetes and lower A1C to the target level. Although initial therapy is aimed at increasing basal insulin supply, usually with intermediate- or long-acting-insulins, patients may also require prandial therapy with short- or rapid-acting insulins (Fig. 1). The very rapid-acting and long-acting insulin analogues have not been shown to lower A1C levels more effectively than the older, rapid-acting or intermediate-acting formulations (71–73). Insulin therapy has beneficial effects on triacylglycerol and HDL cholesterol levels, especially in patients with poor glycemic control (74), but is associated with weight gain of ~2–4 kg, which is probably proportional to the correction of glycemia and predominantly the result of the reduction of glycosuria. Insulin therapy is also associated with hypoglycemia, albeit much less frequently than in type 1 diabetes. In clinical trials aimed at normoglycemia and achieving a mean A1C of ~7%, severe hypoglycemic episodes (defined as requiring help from another person to treat) occurred at a rate of between one and three per 100 patient-years (8,75–77), compared with 61 per 100 patient-years in the DCCT intensive therapy group (4). Insulin analogues with longer, nonpeaking profiles decrease the risk of hypoglycemia modestly compared with NPH, and analogues with very short durations of action reduce the risk of hypoglycemia compared with regular insulin (76,77).

Glucagon-like peptide-1 agonists (exenatide). Glucagon-like peptide-1 (GLP-1) 7–37, a naturally occurring peptide produced by the L-cells of the small intestine, potentiates glucose-stimulated insulin secretion. Exendin-4 has homology with the human GLP-1 sequence but has a longer circulating half-life. It binds avidly to the GLP-1 receptor on the pancreatic β-cell and augments glucose-mediated insulin secretion (32). Synthetic exendin-4 (exenatide) was approved for use in the U.S. in 2005 and is administered twice per day by subcutaneous injection. Although there are less published data on this new compound than the other blood glucose–lowering medications, exendin-4 appears to lower A1C levels by 0.5–1 percentage points, mainly by lowering postprandial blood glucose levels (78–81). Exenatide also suppresses glucagon secretion and slows gastric motility. It is not associated with hypoglycemia but causes a relatively high frequency of gastrointestinal disturbances, with 30–45% of treated patients experiencing one or more episodes of nausea, vomiting, or diarrhea (78–81). These side effects tend to abate over time. In published trials, exenatide is associated with weight loss of ~2–3 kg over 6 months, some of which may be a result of its gastrointestinal side effects. Recent reports have suggested a risk for pancreatitis associated with use of GLP agonists; however, the number of cases is very small and whether the relationship is causal or coincidental is not clear at this time. Currently, exenatide is approved for use in the U.S. with sulfonylurea, metformin, and/or a TZD. Several other GLP-1 agonists and formulations are under development.

Amylin agonists (pramlintide). Pramlintide is a synthetic analogue of the β-cell hormone amylin. It is administered subcutaneously before meals and slows gastric emptying, inhibits glucagon production in a glucose-dependent fashion, and predominantly decreases postprandial glucose excursions (33). In clinical studies, A1C has been decreased by 0.5–0.7 percentage points (82). The major clinical side effects of this drug are gastrointestinal in nature. ~30% of treated participants in the clinical trials have developed nausea, but this side effect tends to abate with time on therapy. Weight loss associated with this medication is ~1–1.5 kg over 6 months; as with exenatide, some of the weight loss may be the result of gastrointestinal side effects. Currently, pramlintide is approved for use in the U.S. only as adjunctive therapy with regular insulin or rapid-acting insulin analogues.

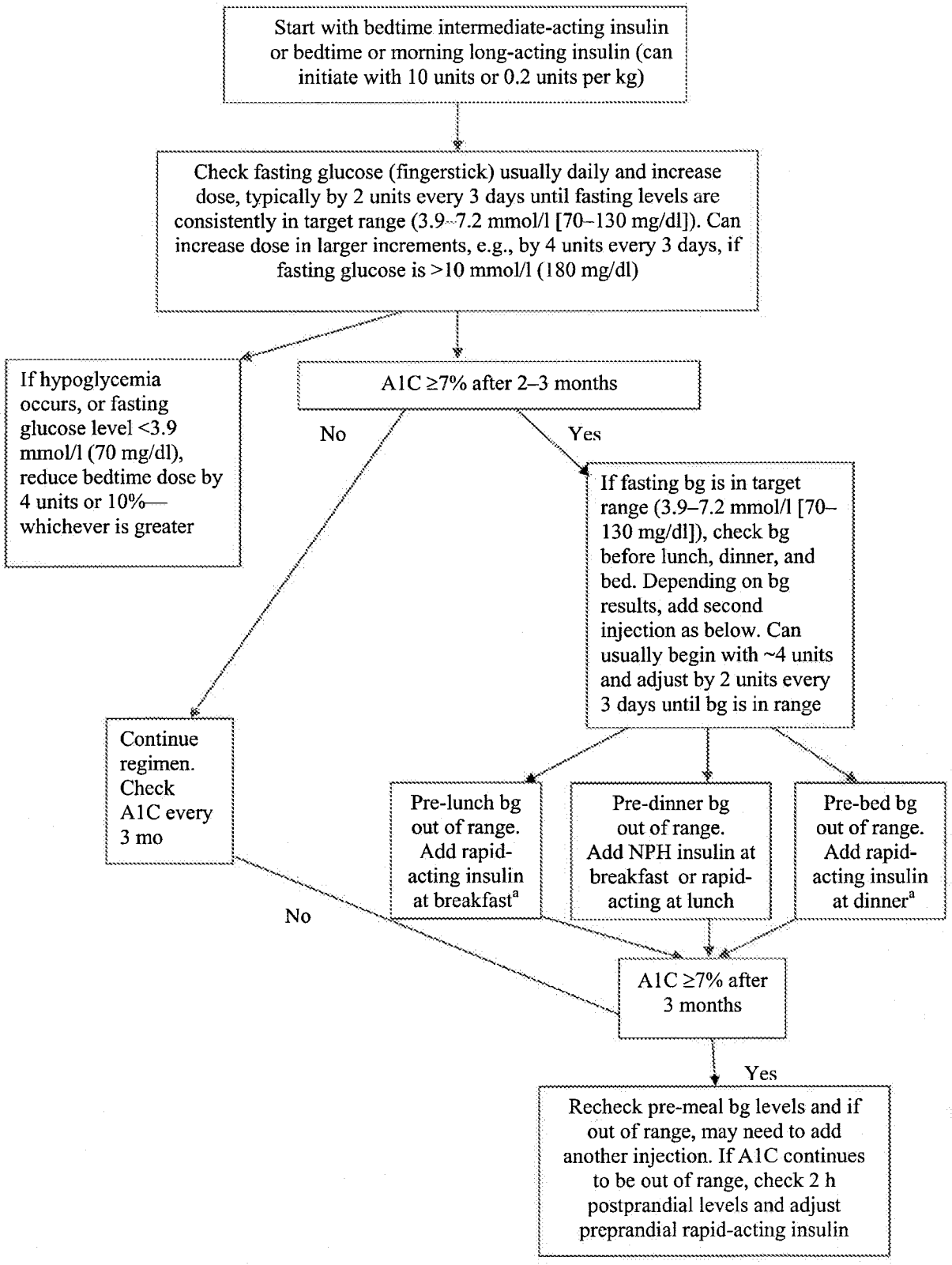

Figure 1—*Initiation and adjustment of insulin regimens. Insulin regimens should be designed taking lifestyle and meal schedule into account. The algorithm can only provide basic guidelines for initiation and adjustment of insulin. See reference 90 for more detailed instructions. [a]Premixed insulins not recommended during adjustment of doses; however, they can be used conveniently, usually before breakfast and/or dinner, if proportion of rapid- and intermediate-acting insulins is similar to the fixed proportions available. bg, blood glucose.*

TITRATION OF METFORMIN

1. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2. After 5–7 days, if gastrointestinal side effects have not occurred, advance dose to 850, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3. If gastrointestinal side effects appear as doses advanced, decrease to previous lower dose and try to advance the dose at a later time.
4. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.
5. Based on cost considerations, generic metformin is the first choice of therapy. A longer-acting formulation is available in some countries and can be given once per day.

Dipeptidyl peptidase four inhibitors. GLP-1 and glucose-dependent insulinotropic peptide (GIP), the main insulinotropic peptides of intestinal origin (incretins), are rapidly degraded by dipeptidyl peptidase four (DPP-4). DPP-4 is a member of a family of cell membrane proteins that are expressed in many tissues, including immune cells (34). DPP-4 inhibitors are small molecules that enhance the effects of GLP-1 and GIP, increasing glucose-mediated insulin secretion and suppressing glucagon secretion (83,84). The first oral DPP-4 inhibitor, sitagliptin, was approved by the Food and Drug Administration in October 2006 for use as monotherapy or in combination with metformin or TZDs. Another DPP-4 inhibitor, vildagliptin, was approved in Europe in February 2008, and several other compounds are under development. In clinical trials performed to date, DPP-4 inhibitors lower A1Clevels by 0.6–0.9 percentage points and are weight neutral and relatively well tolerated (83,84). They do not cause hypoglycemia when used as monotherapy. A fixed-dose combination pill with metformin is available. The potential for this class of compounds to interfere with immune function is of concern; an increase in upper respiratory infections has been reported (34).

How to initiate diabetes therapy and advance interventions

Except in rare circumstances, such as diabetic ketoacidosis or patients who are extremely catabolic or hyperosmolar or who are unable to hydrate themselves adequately (see SPECIAL CONSIDERATIONS/PATIENTS below), hospitalization is not required for initiation or adjustment of therapy. The patient is the key player in the diabetes care team and should be trained and empowered to adjust medications with the guidance of health care professionals to achieve glycemic goals and to prevent and treat hypoglycemia. Many patients may be managed effectively with monotherapy; however, the progressive nature of the disease will require the use of combination therapy in many, if not most, patients over time, to achieve and maintain glycemia in the target range.

The measures of glycemia that are initially targeted on a day-to-day basis are fasting and preprandial glucose levels. Self-monitoring of blood glucose (SMBG) is an important element in adjusting or adding new interventions and, in particular, in titrating insulin doses. The need for and number of required SMBG measurements are not clear (85) and are dependent on the medications used. Oral glucose-lowering regimens that do not include sulfonylureas or glinides, and are therefore not likely to cause hypoglycemia, usually do not require SMBG (86). However, SMBG may be used to determine whether therapeutic blood glucose targets are being achieved and for adjustment of treatment regimens without requiring the patient to have laboratory-based blood glucose testing. Insulin therapy requires more frequent monitoring.

The levels of plasma or capillary glucose (most meters that measure fingerstick capillary samples are adjusted to provide values equivalent to plasma glucose) that should result in long-term glycemia in the nondiabetic target range, as measured by A1C, are fasting and preprandial levels between 3.9 and 7.2 mmol/l (70 and 130 mg/dl). If A1C levels remain above the desired target despite preprandial levels that are in range, postprandial levels, usually measured 90–120 min after a meal, may be checked. They should be <10 mmol/l (180 mg/dl) to achieve A1C levels in the target range.

Attempts to achieve target glycemic levels with regimens including sulfonylureas or insulin may be associated with modest hypoglycemia, with glucose levels in the 3.1–3.9 mmol/l (55–70 mg/dl) range. These episodes are generally well tolerated, easily treated with oral carbohydrate such as glucose tablets or 120–180 ml (4–6 oz) of juice or nondiet soda, and rarely progress to more severe hypoglycemia, including loss of consciousness or seizures.

Algorithm

The algorithm (Fig. 2) takes into account the characteristics of the individual interventions, their synergies, and expense. The goal is to achieve and maintain A1C levels of <7% and to change interventions at as rapid a pace as titration of medications allows when target glycemic goals are not being achieved. Mounting evidence suggests that aggressive lowering of glycemia, especially with insulin therapy, in newly diagnosed diabetes can result in sustained remissions, i.e., normoglycemia without need for glucose-lowering medications (87,88). Type 2 diabetes is a progressive disease (89), and patients should be informed that they are likely to require the addition of glucose-lowering medications over time.

The amylin agonists, α-glucosidase inhibitors, glinides, and DPP-4 inhibitors are not included in the two tiers of preferred agents in this algorithm, owing to their lower or equivalent overall glucose-lowering effectiveness compared with the first- and second-tier agents and/or to their limited clinical data or relative expense (Table 1). However, they may be appropriate choices in selected patients.

Tier 1: well-validated core therapies

These interventions represent the best established and most effective and cost-effective therapeutic strategy for achieving the target glycemic goals. The tier one algorithm is the preferred route of therapy for most patients with type 2 diabetes.

Step 1: lifestyle intervention and metformin. Based on the numerous demonstrated short- and long-term benefits that accrue when weight loss and increased levels of activity are achieved and maintained, as well as the cost-effectiveness of lifestyle interventions when they succeed,

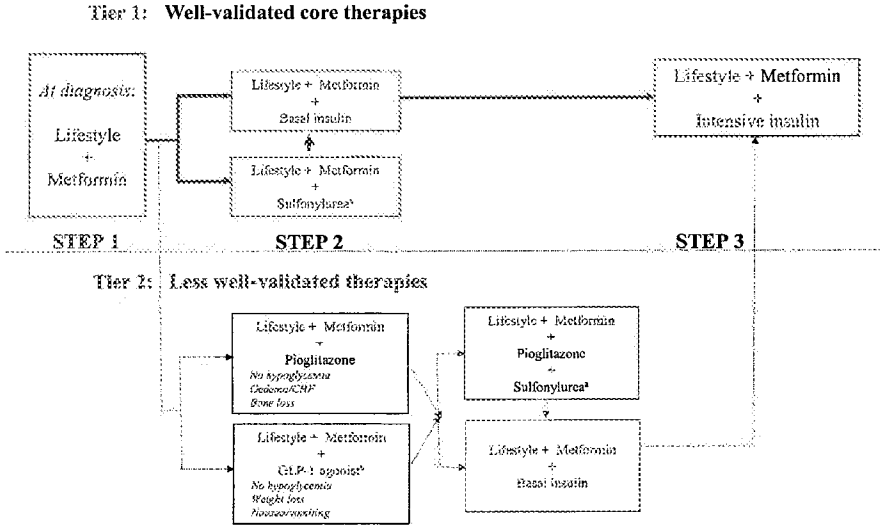

Figure 2—*Algorithm for the metabolic management of type 2 diabetes; Reinforce lifestyle interventions at every visit and check A1C every 3 months until A1C is <7% and then at least every 6 months. The interventions should be changed if A1C is ≥7%. [a]Sulfonylureas other than glyburide (glyburide) or chlorpropamide. [b]Insufficient clinical use to be confident regarding safety. See text box, entitled TITRATION OF METFORMIN. See Fig. 1 for initiation and adjustment of insulin. CHF, congestive heart failure.*

the consensus is that lifestyle interventions should be initiated as the first step in treating new-onset type 2 diabetes (Fig. 2). These interventions should be implemented by health care professionals with appropriate training—usually registered dietitians experienced in behavioral modification—and be sensitive to ethnic and cultural differences among populations. Moreover, lifestyle interventions to improve glucose, blood pressure, and lipid levels, and to promote weight loss or at least avoid weight gain, should remain an underlying theme throughout the management of type 2 diabetes, even after medications are used. For the 10–20% of patients with type 2 diabetes who are not obese or overweight, modification of dietary composition and activity levels may play a supporting role, but medications are still generally required early in the course of diabetes (see SPECIAL CONSIDERATIONS/PATIENTS below).

The authors recognize that for most individuals with type 2 diabetes, lifestyle interventions fail to achieve or maintain the metabolic goals either because of failure to lose weight, weight regain, progressive disease, or a combination of factors. Therefore, our consensus is that metformin therapy should be initiated concurrently with lifestyle intervention at diagnosis. Metformin is recommended as the initial pharmacological therapy, in the absence of specific contraindications, for its effect on glycemia, absence of weight gain or hypoglycemia, generally low level of side effects, high level of acceptance, and relatively low cost. Metformin treatment should be titrated to its maximally effective dose over 1–2 months, as tolerated (see text box, entitled Titration of Metformin). Rapid addition of other glucose-lowering medications should be considered in the setting of persistent symptomatic hyperglycemia.

Step 2: addition of a second medication. If lifestyle intervention and the maximal tolerated dose of metformin fail to achieve or sustain the glycemic goals, another medication should be added within 2–3 months of the initiation of therapy or at any time when the target A1C level is not achieved. Another medication may also be necessary if metformin is contraindicated or not tolerated. The consensus regarding the second medication added to metformin was to choose either insulin or a sulfonylurea (Fig. 2). As discussed above, the A1C level will determine in part which agent is selected next, with consideration given to the more effective glycemia-lowering agent, insulin, for patients with an A1C level of >8.5% or with symptoms secondary to ehyperglycemia. Insulin can be initiated with a basal (intermediate- or long-acting) insulin (see Fig. 1 for suggested initial insulin regimens) (90). However, many newly diagnosed type 2 diabetic patients will usually respond to oral medications, even if symptoms of ehyperglycemia are present (48).

Step 3: further adjustments. If lifestyle, metformin, and sulfonylurea or basal insulin do not result in achievement of target glycemia, the next step should be to start, or intensify, insulin therapy (Fig. 1). Intensification of insulin therapy usually consists of additional injections that might include a short- or rapid-acting insulin given before selected meals to reduce postprandial glucose excursions (Fig. 1). When insulin injections are started, insulin secretagogues (sulfonylurea or glinides) should be discontinued, or tapered and then discontinued, since they are not considered to be synergistic. Although addition of a third oral agent can be considered, especially if the A1C level is close to target (A1C <8.0%), this approach is usually not preferred, as it is no more effective in lowering glycemia, and is more costly, than initiating or intensifying insulin (91).

Tier 2: less well-validated therapies

In selected clinical settings, this second-tier algorithm may be considered. Specifically, when hypoglycemia is particularly undesirable (e.g., in patients who have hazardous jobs), the addition of exenatide or pioglitazone may be considered. Rosiglitazone is not recommended. If promotion of weight loss is a major consideration and the A1C level is close to target (<8.0%), exenatide is an option. If these interventions are not effective in achieving target A1C, or are not tolerated, addition of a sulfonylurea could be considered. Alternatively, the tier two interventions should be stopped and basal insulin started.

Rationale for selecting specific combinations

More than one medication will be necessary for the majority of patients over time. Selection of the individual agents should be made on the basis of their glucose-lowering effectiveness and other characteristics listed in Table 1. However, when adding second antihyperglycemic medications, the synergy of particular combinations and other interactions should be considered. In general, antihyperglycemic drugs with different mechanisms of action will have the greatest synergy. Insulin plus metformin (92) is a particularly effective means of lowering glycemia while limiting weight gain.

Special considerations/patients

In the setting of severely uncontrolled diabetes with catabolism, defined as fasting plasma glucose levels >13.9 mmol/l (250 mg/dl), random glucose levels consistently above 16.7 mmol/l (300 mg/dl), A1C above 10%, or the presence of ketonuria, or as symptomatic diabetes with polyuria, polydipsia and weight loss, insulin therapy in combination with lifestyle intervention is the treatment of choice. Some patients with these characteristics will have unrecognized type 1 diabetes; others will have type 2 diabetes with severe insulin deficiency. Insulin can be titrated rapidly and is associated with the greatest likelihood of returning glucose levels rapidly to target levels. After symptoms are relieved and glucose levels decreased, oral agents can often be added and it may be possible to withdraw insulin, if preferred.

Conclusions

Type 2 diabetes is epidemic. Its long-term consequences translate into enormous human suffering and economic costs; however, much of the morbidity associated with long-term microvascular and neuropathic complications can be substantially reduced by interventions that achieve glucose levels close to the nondiabetic range. Although new classes of medications and numerous combinations have been demonstrated to lower glycemia, current-day management has failed to achieve and maintain the glycemic levels most likely to provide optimal healthcare status for people with diabetes.

Summary

The guidelines and treatment algorithm presented here emphasize the following:

- Achievement and maintenance of near normoglycaemia (A1C <7.0%)
- Initial therapy with lifestyle intervention and metformin
- Rapid addition of medications, and transition to new regimens, when target glycemic goals are not achieved or sustained
- Early addition of insulin therapy in patients who do not meet target goals

Duality of interest

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